CHEMICAL REVIEWS

VOLUME 36

CONTENTS

THE CHEMISTRY OF COUMARINS

SURESH M. SETHNA

Elphinstone College, Bombay, India

AND

NARSINH M. SHAH

*M. R. Science Institute, Gujarat College, Ahmedabad, India*

CONTENTS

I. INTRODUCTION

The fusion of a pyrone ring with a benzene nucleus gives rise to a class of heterocyclic compounds known as benzopyrones, of which two distinct types are recognized: (*1*) benzo-α-pyrones, commonly called coumarins, and (*2*) benzo-γ-pyrones, called chromones, the latter differing from the former only in the position of the carbonyl group in the heterocyclic ring.
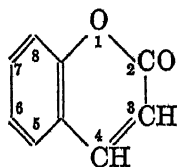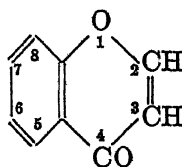
Benzo-α-pyrone   Benzo-γ-pyrone

Representatives of these groups of compounds are found to occur in the vegetable kingdom, either in the free or in the combined state. Coumarin, the parent substance of the benzo-α-pyrone group, was first isolated from tonka beans in 1820. Several coumarin derivatives have been found to be widely distributed in the plant kingdom. Particularly the plants belonging to the natural orders of Orchidaceae, Leguminoceae, Rutaceae, Umbelliferae, and Labiatae are rich sources of naturally occurring coumarins (224).

Coumarin was initially considered to be a benzoic acid derivative, but its synthesis by W. H. Perkin, Sr., (160) from salicylaldehyde by means of his classical reaction established its relation to o-hydroxycinnamic acid, which loses a molecule of water in forming the lactone ring.

However, different constitutional formulae have been suggested from time to time. Of the various formulae proposed by Perkin (I), Basecke (II), Strecker, Fittig, and Tiemann (III), Salkowski (IV), and Morgan and Micklethwait (V), formula III has been found to be in complete accord with the known reactions of the coumarin derivatives and has been universally accepted as correct (vide Hugo Schiff (179)).
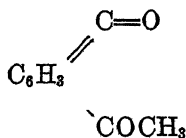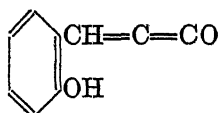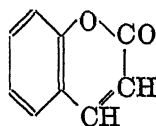
	II	III
Perkin (1868)	Basecke (1870)	Strecker (1867)
		Fittig (1868)
		Tiemann (1877)
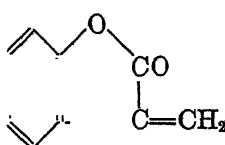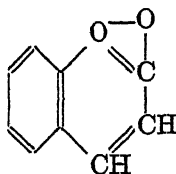
IV
Salkowski (1877)   Morgan and Micklethwait (1906)
Clayton (1908)

Thus coumarins and their derivatives are, from the point of view of their chemical constitution, a group of lactones derived from o-hydroxycinnamic acids: alternately stated, a coumarin ring system is formed by the fusion of a benzene and a 1,2-pyrone ring, i.e., coumarins are a class of heterocyclic compounds containing oxygen as a member of the heterocyclic ring.

II. METHODS FOR THE SYNTHESIS OF COUMARIN DERIVATIVES

Of the number of synthetic methods, there are a few which have yielded important results; there are several others whose applications are less general. All these methods center round the possibility of building up the pyrone ring on a suitable benzene derivative.

(1) Perkin reaction: This classical method has entered into every textbook of organic chemistry. As stated above, Perkin (160) first synthesized coumarin from salicylaldehyde by heating it with acetic anhydride and anhydrous sodium acetate:

$$\text{(salicylaldehyde)} + (CH_3CO)_2O + CH_3COONa \rightarrow$$

$$\text{(o-hydroxycinnamate)} \quad CH=CHCOONa \rightarrow \text{(coumarin)}$$
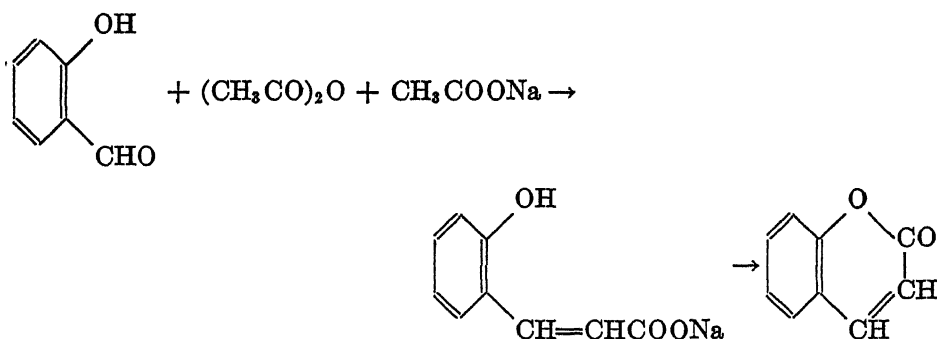
This reaction occurs with the formation of an intermediate o-hydroxycinnamic acid derivative which passes spontaneously into the lactone when liberated from its sodium salt. This method was successfully used by Tiemann and Herzfield (256), Taage (251), and, later on, by numerous workers in the field. In recent years, E. Späth (224) has utilized this reaction to synthesize several naturally occurring coumarins. It has, however, its limitations: the appropriate initial o-hydroxyaldehydes are rather difficult to obtain from many substituted phenols; the method gives coumarins unsubstituted in the pyrone ring; the yields obtained are also low. Yanagisawa and Kondo (270) claim to have improved the yields by using iodine as a catalyst in the reaction.

Dyson (81) obtained 3,3'-dicoumarin as the sole product of the reaction between salicylaldehyde, acetic anhydride, and sodium succinate instead of the expected coumarin-3-acetic acid. Dey and Sankaranarayanan (76) replaced acetic anhydride by succinic anhydride and obtained the coumarin-3-acetic acid in good yield.

The Perkin reaction on o-vanillin for the synthesis of 8-methoxycoumarin leads to the production of the *trans* form of 2-hydroxy-3-methoxycinnamic acid in large quantity (67); this cinnamic acid derivative does not undergo ring closure to the coumarin.

(2) *Pechmann reaction:* Pechmann (152) found that a coumarin derivative is formed when a mixture of a phenol and malic acid is heated in the presence of concentrated sulfuric acid:

$$\text{HO}\text{—}\text{(phenol)}\text{—}\text{OH} + \begin{array}{l} COOH \\ | \\ CH_2CH(OH)COOH \end{array} \xrightarrow{H_2SO_4} \text{(coumarin)} + 3H_2O + CO$$
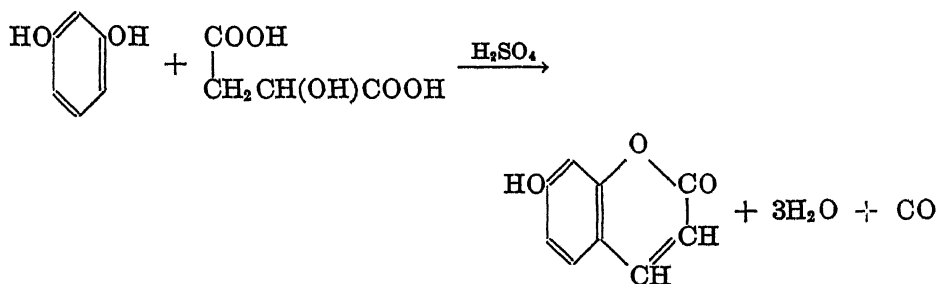
This method has limited applicability. Many substituted phenols do not undergo this reaction; only coumarins unsubstituted in the pyrone ring are obtained.

(3) *Pechmann–Duisberg reaction:* Pechmann and Duisberg (154) found that phenols condense with β-ketonic esters in the presence of sulfuric acid, giving coumarin derivatives:

$$R \langle \text{benzene} \rangle OH + \begin{array}{c} CH_3 COCH_2 COOC_2H_5 \\ \downarrow \\ CH_3 C(OH){=}CHCOOC_2H_5 \end{array} \rightarrow$$

$$R \langle \text{ring} \rangle \begin{array}{c} O \\ CO \\ CH \\ C \\ CH_3 \end{array} + C_2H_5OH + H_2O$$
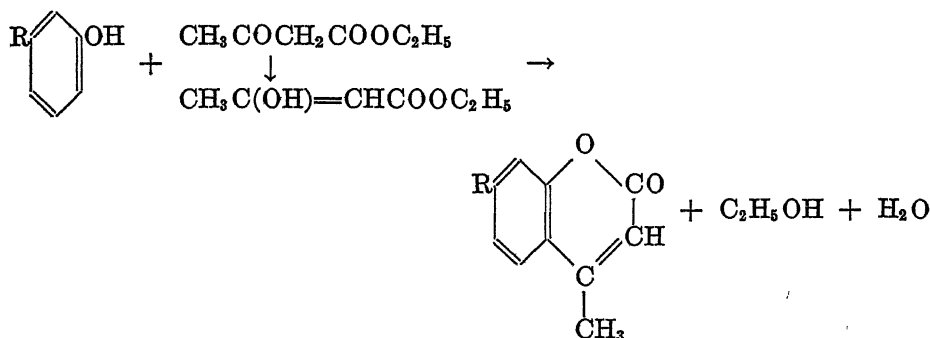
This reaction has found extensive applications in the synthesis of various coumarin derivatives. It gives coumarins substituted in the pyrone ring. The various factors affecting the course of this reaction have been separately discussed (*vide infra*).

(4) *Knoevenagel reaction:* Knoevenagel (120) developed a method for the synthesis of coumarin derivatives from *o*-hydroxyaldehydes by condensation with ethyl malonate, ethyl acetoacetate, ethyl cyanoacetate, etc., in the presence of piperidine, pyridine, and other organic bases:

$$HO \langle \text{ring} \rangle \begin{array}{c} OH \\ CHO \end{array} + \begin{array}{c} COOC_2H_5 \\ | \\ CH_2R \end{array} \rightarrow HO \langle \text{ring} \rangle \begin{array}{c} O \\ CO \\ CR \\ CH \end{array}$$

(R = COOC₂H₅, COCH₃)

This reaction has been successfully used by various workers, notably by Shah and Shah (200), to prove the ortho position of the formyl group to the hydroxyl group in their studies on γ-substitution in the resorcinol nucleus. They have synthesized a large number of coumarin derivatives by this method by the condensation of formylated 4-acylresorcinols and other di- and tri-hydroxyacetophenones with malo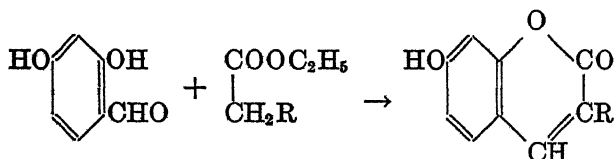nic ester, acetoacetic ester, and cyanoacetic ester. This method has been found to be better than the Perkin–Robinson method (163) of pyrylium salt formation on account of the smoothness with which it works.

o-Hydroxyaldehydes and phenyl acetonitrile condense in the presence of sodium ethoxide or alcoholic potash, giving 3-phenylcoumarins (29, 118):

$$CH_3O \langle \text{ring} \rangle \begin{array}{c} OH \\ CHO \end{array} + \begin{array}{c} CN \\ | \\ CH_2 \\ | \\ C_6H_5 \end{array} \rightarrow CH_3O \langle \text{ring} \rangle \begin{array}{c} O \\ CO \\ CC_6H_5 \\ CH \end{array}$$
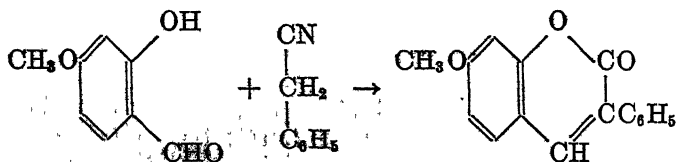
Pandya and his coworkers (126) have investigated the Knoevenagel reaction with various aldehydes in the presence of pyridine alone and have found that a trace of pyridine is efficacious in bringing about the condensation with nearly theoretical yields. Thus pyridine in traces is quite comparable to Knoevenagel's famous reagent piperidine in traces. In a series of papers, Pandya and his coworkers (117) have investigated many other bases, which have been found to possess a similar efficiency in promoting these reactions. They have also made a study of constitutional factors by using differently substituted aldehydes. Pandya and Sodhi (148) have obtained 3-aminocoumarin in excellent yield by condensing salicylaldehyde with glycine in the presence of a trace of pyridine.

Ghosal (91) found that the reaction between an o-hydroxybenzaldehyde and ω-cyanoacetophenone in the presence of hydrogen chloride gives a benzoylcoumarin instead of the expected pyrylium derivative.
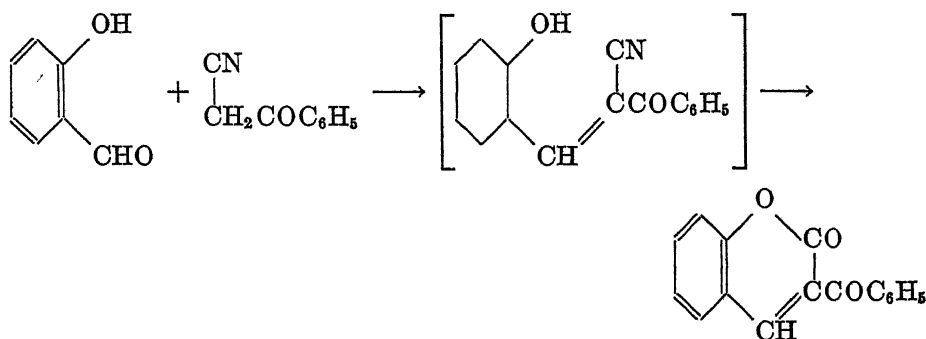
(5) Sonn (222) found that resorcinol condenses with cyanoacetic ester under the conditions of the Hoesch reaction (106); the ketimine hydrochloride obtained on hydrolysis gives ultimately 4,7-dihydroxycoumarin:
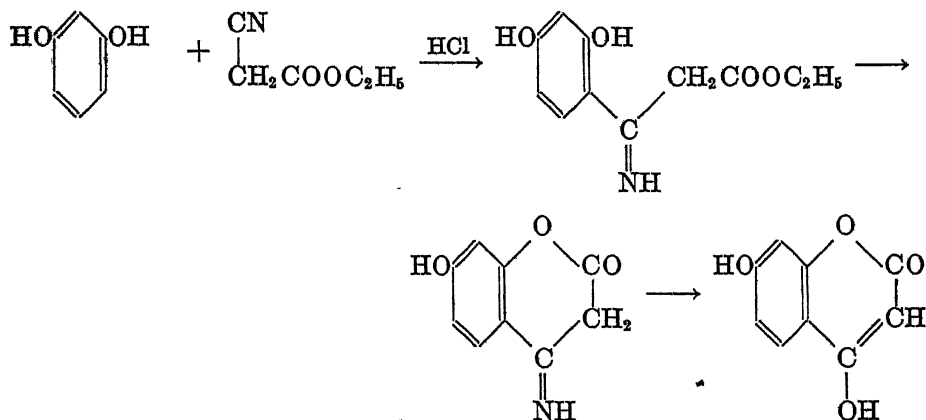
Still another method by which 4-hydroxycoumarins are obtained is due to Anschütz (7, 8), who condensed the sodium derivative of acetoacetic ester with o-acetoxybenzoyl chloride in ethereal solution and obtained 4-hydroxycoumarin

derivatives. He extended his work by using the sodium derivatives of malonic ester and cyanoacetic ester with various substituted acid chlorides. Heilbron and Hill (103) have obtained 3-methyl-, 3-benzoyl-, and 3-benzyl-coumarins by this method.
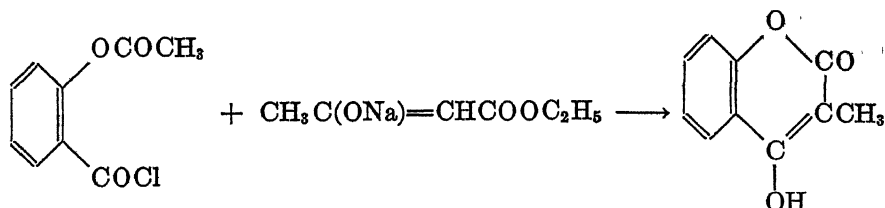
Pauly and Lockemann (151) synthesized 4-hydroxycoumarin from methyl acetylsalicylate by adding metallic sodium to the molten ester. Several 3-substituted 4-hydroxycoumarins have also been prepared by Stahmann et al. (249) from acylated derivatives of methyl salicylate.

(6) Weiss and Merksammer (261) found that resacetophenone on condensation with ethyl ethoxymethyleneacetoacetate by heating with alcoholic sodium ethoxide gave 7-hydroxy-3,6-diacetylcoumarin. Weiss and Kratz (260) extended the method and found that ethyl ethoxymethylenemalonate similarly condensed to give coumarin-3-carboxylates from resorcinol derivatives, the carbethoxyl group having hydrolyzed to the carboxyl group.
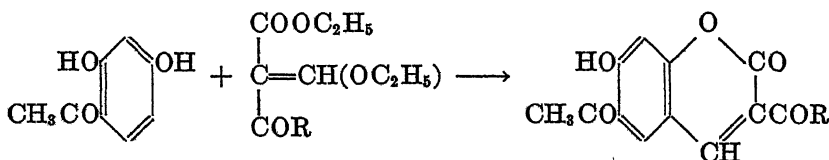
($R = CH_3$, OC_2H_5, OH)

(7) Baker et al. (12) found that α-formylphenylacetonitrile and its derivatives condense with resorcinol and other phenols, in the presence of phosphorus oxychloride or dry hydrogen chloride as condensing agent, leading to the production of 3-phenylcoumarins in poor yields and not the isomeric 3-phenylchromones (isoflavones):
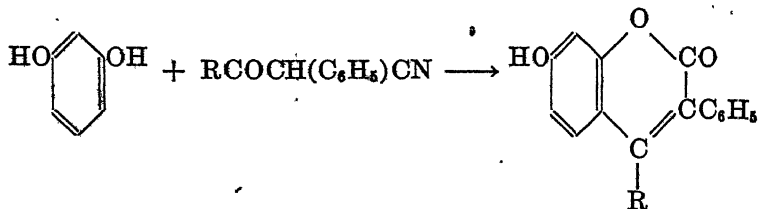
($R = CH_3$, H, C_2H_5)

(8) One more method of general applicability but of limited interest has been put forward by Smith and his collaborators. Smith and Dobrovolny (219) showed that 3-carbethoxy-5,7,8-trimethyl-6-hydroxycoumarin was produced when duroquinone reacted with ethyl sodiomalonate in benzene solution.
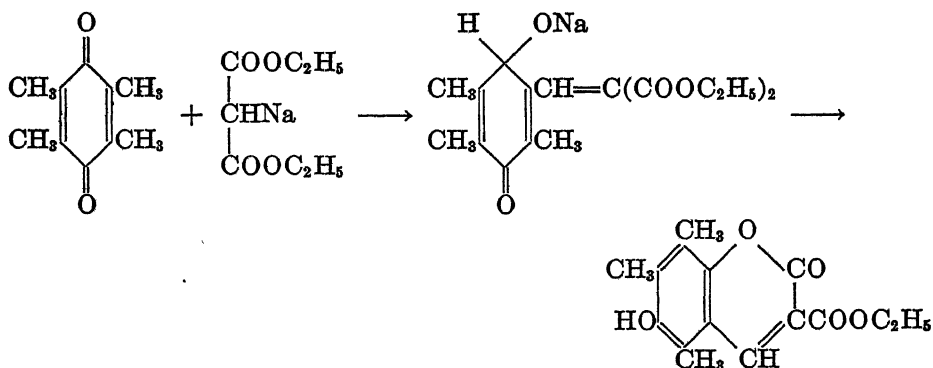
This reaction between completely methylated quinones and sodium enolates appears to be a promising method for the synthesis of 6-hydroxy-5,7,8-trimethyl-coumarins substituted in the 3-position by such groups as carbethoxyl, acyl, cyano, etc. Smith and coworkers (216, 217, 218, 220) have exhaustively investigated this reaction with various brominated methylquinones and found that they may react with a metallic enolate to produce either a coumarin by reaction with a methyl group or a quinone malonic ester by direct replacement of a bromine atom.

(9) Chakravarti and Majumdar (44) have developed a method by which 3,4-dialkyl-substituted coumarins not available by the usual methods may be synthesized: o-hydroxyaryl alkyl ketones, under the conditions of the Reformatsky reaction, are ultimately converted into coumarin derivatives.
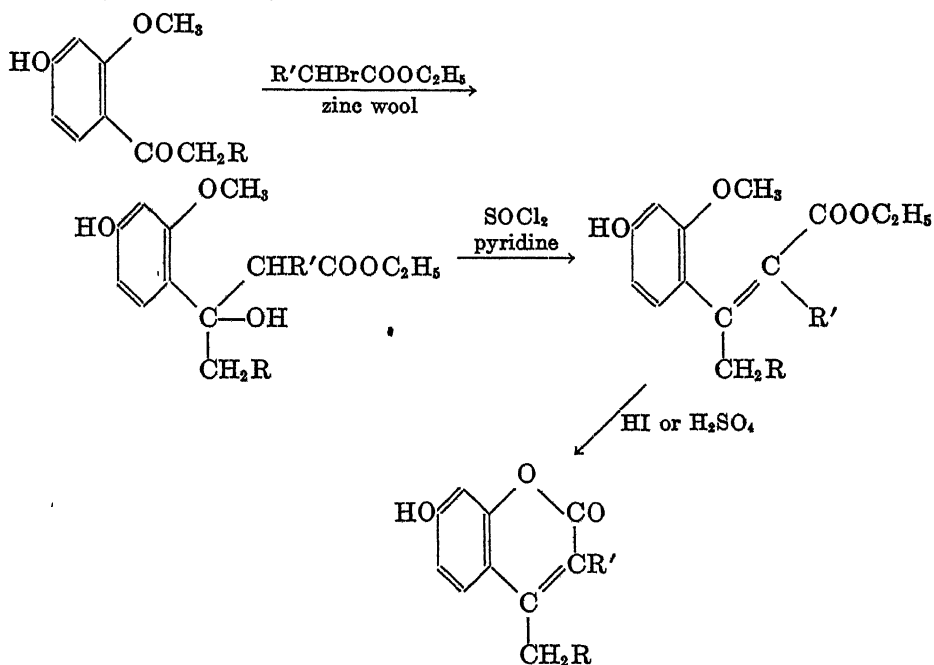
(R = R' = H or alkyl)

In their attempts to synthesize some coumarins by this method, the same authors found that (1) when there are two alkyl substituents, namely, in the α- and β-positions of the expected cinnamic acid, a *cis* acid is formed, which can be easily cyclized to the coumarin derivative in quantitative yield; (2) when there is no substituent in the α- or β-position or only one in the α-position of the expected cinnamic acid, a *trans* acid, i.e., o-coumaric acid, is formed and the coumarin ring closure does not take place. Further, they found that methyl ethers of o-hydroxyaldehydes when subjected to the above reaction also gave *trans*-cinnamic acids, which could not be converted into coumarins.

(10) Recently Bert (27) has developed a general method for synthesizing coumarins, which consists in condensing phenolic ethers with $CH_2ClCH=CHCl$ either by the Friedel–Crafts reaction or in the presence of zinc dust to obtain $ROC_6H_4CH_2CH=CHCl$, which can also be synthesized by condensing $CH_2ClCH=CHCl$ with o-bromophenolic ether through the Grignard reaction. This is then converted into the corresponding coumarin in two ways, as shown below:
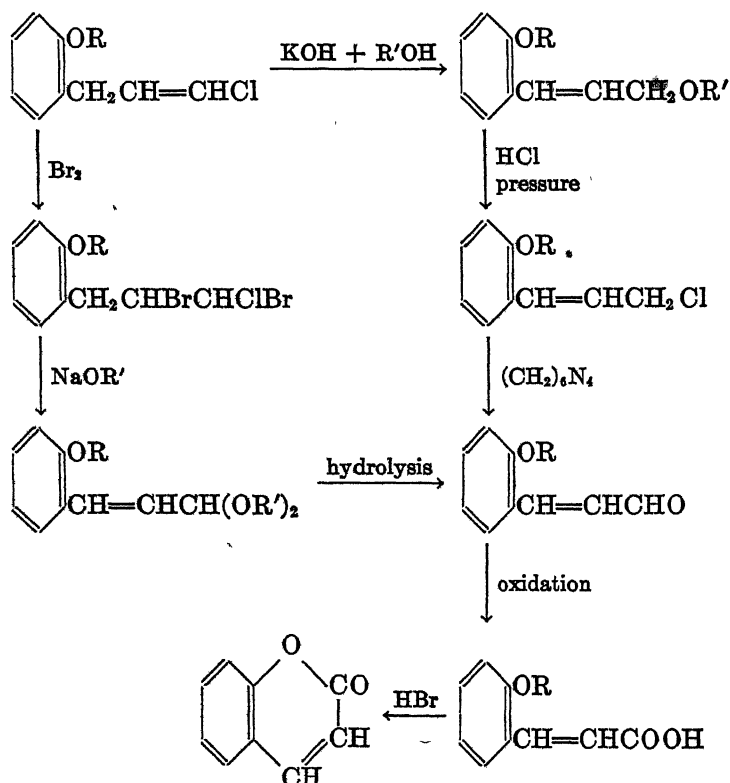
(11) *Kostanecki acylation of o-hydroxyketones:* This is a method of coumarin formation with an element of uncertainty in it. Kostanecki and Rozycki (121) showed that the products obtained by Nagai (144) and Tahara (252) by heating

resacetophenone and its monomethyl ether with acetic anhydride and sodium acetate were chromone derivatives. This method was further developed by Allan and Robinson (6) for the synthesis of a large number of chromones and chromonols occurring in nature.

It has been found, however, that this method is not exclusively applicable for chromone formation, inasmuch as chromones or coumarins or a mixture of both may result from the above reaction, since there are two ways in which the intermediate acyl derivative may lose water, giving a chromone or a coumarin:

Chromone

Coumarin

(R = H or alkyl)
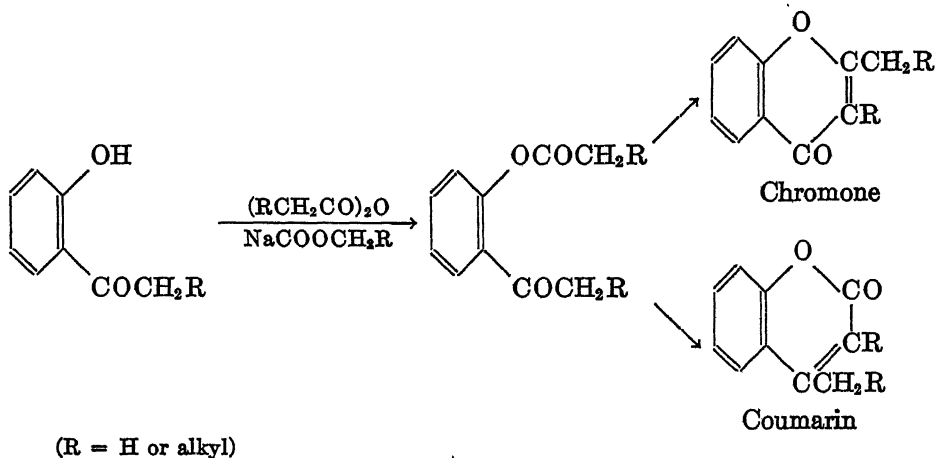
Wittig (268) found that the Kostanecki acetylation of 4-chloro-6-acetylphenol leads to the production of a mixture of 6-chloro-4-methylcoumarin and 6-chloro-2-methylchromone. Later, he and his coworkers (269) isolated 2-methylchromone and 4-methylcoumarin in the Kostanecki acetylation of o-hydroxyacetophenone. Bargenilli (23) and Baker and Eastwood (17) showed that the use of phenylacetic anhydride and sodium phenylacetate in the Kostanecki reaction leads to coumarin and not chromone formation.

Heilbron and his collaborators (100, 101, 102) have also investigated this reaction and shown that the coumarins are formed as by-products. Chakravarti and coworkers (40, 45) have shown by a detailed study of the Kostanecki reaction on halogenated aceto-, propio-, and butyro-phenones that the halogen atom has no marked influence upon chromone formation.

Recently, Sethna and Shah (197) have studied the Kostanecki acylation of orcacetophenone and its monomethyl ether and have shown the exclusive formation of a coumarin. However, γ-orcacetophenone has been found to give on Kostanecki acetylation a mixture consisting mainly of chromone and a small quantity of coumarin (63). Trivedi, Sethna, and Shah (258) similarly investigated orcpropiophenone, which on acylation has been found to give exclusively chromones.

The formation of coumarin or chromone in this reaction is dependent not only on the acid anhydride and the salt used but also on the nature of the

o-hydroxyphenyl ketone. When sodium acetate and acetic anhydride are used, the introduction of higher alkyl substituents in the side chain of the hydroxy-ketone favors chromone formation: e.g., resacetophenone gives chromone; res-propiophenone also gives chromone (32). Chadha, Mahal, and Venkatraman (36) find that an ω-substituent in an *o*-hydroxyaryl methyl ketone favors chro-mone formation. They also find that chromone formation takes place as a rule more readily in the naphthalene than in the benzene series.

The ketone being the same, if the anhydride and the sodium salts of higher acids like propionic and butyric acids are taken, there is a tendency towards coumarin formation.

When benzoic anhydride and sodium benzoate or their derivatives are used, the products obtained are always flavone derivatives (2-phenylchromones); with phenylacetic anhydride or acetic anhydride and sodium phenylacetate the products formed are mostly 3-phenylcoumarin derivatives. In the case of *o*-hydroxybenzophenones, only 4-phenylcoumarin derivatives are formed.

III. PECHMANN CONDENSATION OF β-KETONIC ESTERS WITH PHENOLS

A rapid development in the chemistry of coumarins is due mainly to the syn-thetic method universally known as the Pechmann reaction, which consists in reacting phenols with β-ketonic esters in the presence of sulfuric acid. As stated before, this elegant method has found extensive application. However, the course of the reaction is influenced by all the factors: *viz.*, (*1*) the nature of the phenol, (*2*) the nature of the β-ketonic ester, and (*3*) the condensing agent.

A. EFFECT OF SUBSTITUENTS IN THE PHENOL AND THE β-KETONIC ESTERS

Pechmann and Duisberg condensed resorcinol, phenol, and *p*-cresol with aceto-acetic ester and its α-methyl derivative; then they extended the reaction to *o*-cresol, pyrogallol, orcinol, phloroglucinol, and α- and β-naphthols. They found that *m*-dihydroxyphenols and α-naphthol condensed readily, giving good yields of coumarins, while monohydric phenols and β-naphthol failed to give anything but poor yields. Fries and Klostermann (84) also found that while the formation of coumarins from phenol, *o*-cresol, and *p*-cresol under the condi-tions of the Pechmann reaction proceeds with difficulty, it takes place readily with *m*-cresol. Pechmann and Maxshaal (159) condensed various aminophenols, using anhydrous zinc chloride instead of sulfuric acid as condensing agent. It was observed that *m*-diethylaminophenol condensed more readily than the iso-meric *o*- and *p*-derivatives. Pechmann and Hancke (156) obtained 3-chloro-coumarins by the Pechmann condensation of ethyl α-chloroacetoacetate with phenols.

Various workers have studied the Pechmann reaction, using various sub-stituted phenols and different β-ketonic esters. Biginelli (28) condensed quinol with ethyl oxalacetate in the presence of sulfuric acid and obtained 6-hydroxy-coumarin-4-carboxylic acid. Pechmann with Kraft (157) and Graeger (155) extended this reaction to other phenols. Dey (64) condensed various phenols with acetonedicarboxylic acid ester and made a systematic study of the reac-tivity of the coumarin-4-acetic acids thus synthesized:

$$HO-\!\!\!\bigcirc\!\!\!-OH \quad + \quad \begin{matrix} COOC_2H_5 \\ | \\ CH_2 \\ | \\ COCH_2COOC_2H_5 \end{matrix} \quad \longrightarrow \quad HO-\!\!\!\bigcirc\!\!\!\begin{matrix} O \\ CO \\ CH \\ C \\ | \\ CH_2COOC_2H_5 \end{matrix}$$
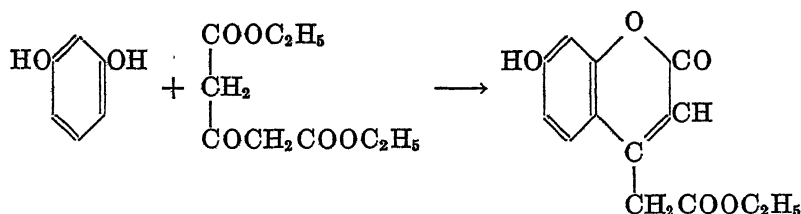
Clayton (48) found that the phenols with alkyl, hydroxy, and dialkylamino groups in the positions marked X in the formulas given below undergo condensa-

$$X-\!\!\!\bigcirc\!\!\!-OH \qquad\qquad X-\!\!\!\bigcirc\!\!\!\begin{matrix} X \\ OH \end{matrix}$$

tion with β-ketonic esters, giving good yields of coumarins. Chlorine as a substituent in these positions has a similar effect but to a less appreciable extent. The introduction of such substituents as nitro, carboxyl, carbethoxyl, and acetyl prevents the condensation. This generalization is based on Clayton's own work and on that of previous investigators on substituted monohydric phenols, which are known to be less reactive than the polyhydric phenols.

An exception to the above rule is met with in the case of oxalacetic ester and quinol, as mentioned above. This is rather interesting, as quinol condenses with other β-ketonic esters with difficulty. m-Cresol reacts very feebly with this ester; pyrogallol and orcinol give no coumarins with it.

Recently some work has been done on the influence of substituents on the reactivity of the resorcinol nucleus in the Pechmann condensation. Chakravarti and his coworkers (41, 43) found that 2-nitro- and 4-nitro-resorcinols readily condense with acetoacetic ester to give 7-hydroxycoumarin derivatives. On condensing the same phenols with α-alkylacetoacetates, they found that 2-nitroresorcinol condensed with α-methylacetoacetate but failed to condense with α-ethyl- and other higher α-alkyl-acetoacetates. 4-Nitroresorcinol did not condense even with α-methylacetoacetate. Thus the presence of a nitro group in the resorcinol nucleus greatly depresses its reactivity, and a nitro group in the 4-position inhibits the Pechmann reaction more than a nitro group in the 2-position.

Chakravarti and Ghosh (43) also condensed 4-chlororesorcinol with various β-ketonic esters and obtained 6-chloro-7-hydroxycoumarin derivatives in all cases, the condensation taking place readily.

Shah et al. (208) found that methyl β-resorcylate condenses with ethyl acetoacetate, giving a 7-hydroxycoumarin derivative. Sethna and Shah (195) extensively studied the reaction of this phenolic ester with several substituted β-ketonic esters and obtained coumarins in all cases, a result which shows that a 4-carbomethoxy group in the resorcinol nucleus has but little retarding influence on the course of the Pechmann reaction. The same authors (198) have also condensed p-orsellinic acid with ethyl acetoacetate and obtained 7-hydroxy-4,5-dimethyl-coumarin-8-carboxylic acid; this result is very interesting as, on decarboxylation,

7-hydroxy-4,5-dimethylcoumarin, which cannot be obtained ordinarily by the condensation of orcinol with acetoacetic ester (51), was easily synthesized.

Sethna (192) condensed methyl phloroglucinolcarboxylate with acetoacetic ester and obtained methyl 5,7-dihydroxy-4-methylcoumarin-6(or 8)-carboxylate, but the free acid could not be condensed as it decomposes into phloroglucinol and carbon dioxide. γ-Resorcylic acid easily condenses with ethyl acetoacetate under the usual conditions of the Pechmann reaction.

A 4-acyl group in the resorcinol nucleus completely inhibits the Pechmann condensation, as resacetophenone does not condense with acetoacetic ester in the presence of sulfuric acid or sodium ethoxide, while 2-acylresorcinols present no such difficulty and easily condense with various β-ketonic esters, giving 7-hydroxy-8-acylcoumarin derivatives (129, 204). The qualitative order of the above groups with regard to the deactivating effect is therefore

$$—COCH_3 > —NO_2 > —COOCH_3$$

Desai and Mavani (62) have studied various substituted pyrogallol derivatives with a view to ascertaining their reactivity in the Pechmann condensation. They found that all the above groups exercise an inhibiting effect to a varying extent. The same authors have investigated the quinol derivatives with a similar object. The presence of acetyl and halogen substituents exerts an inhibiting effect, while alkyl groups exert no such retarding influence.

From the above results, a plausible explanation on the basis of the electronic conception can be advanced for the capacity of phenols and their substitution products to undergo coumarin condensation with β-ketonic esters (60). The feeble power possessed by ordinary phenol is enhanced by the presence of electron-donating groups in the meta position, e.g., CH_3, OH, OCH_3, NH_2 etc., but is depressed and almost annihilated by electron-attracting groups in the same position, e.g., NO_2, SO_3H, $COOH$, $COOCH_3$, CHO, etc. Thus, resorcinol derives its extraordinary power to undergo coumarin condensation at position 4 (the 4- and 6-positions are identical) from the accession of electrons from the additional hydroxyl group in position 1, which is para to the point of attack. This activation of position 4 is so great that even the presence of electron-attracting groups at the 2- or 6-position is not sufficient to destroy this power. When position 6 is occupied by groups which are electron sinks, the resorcinol forms
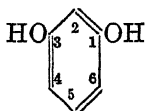
coumarins with difficulty, while groups which are electron sources do not seriously interfere with this property. Moreover, as 2-substituted resorcinols form coumarins easily but 4-substituted ones do not, it follows that electron sinks exercise a greater deactivating influence at position 4 than at position 2.

So far we have mainly considered the effect of different substituents in the phenolic nucleus. We shall now consider the different substituents in the acetoacetic ester molecule with regard to their effect on the course of the Pechmann reaction.

Several α-substituted acetoacetates with simple alkyl groups like methyl, ethyl, propyl, butyl, allyl, and benzyl have been investigated from time to time. In the case of reactive phenols like resorcinol, pyrogallol, phloroglucinol, orcinol, and α-naphthol, coumarins are obtained more or less readily irrespective of the substituent in the ester used. In the case of m-cresol, the unsubstituted ester gives coumarin but on the introduction of α-substituents in the ester molecule, the yield begins to decrease and as the propyl group is introduced, the reaction is inhibited altogether. It is interesting to note, however, that α-allylaceto-acetate gives a coumarin with m-cresol easily (145). m-Cresol does not give a coumarin with α-phenylacetoacetate when sulfuric acid is used as condensing agent. In the case of less reactive phenols, such as phenol, p-cresol, quinol, β-naphthol, etc., the unsubstituted acetoacetate gives coumarins in poor yield. The introduction of an α-alkyl group has a retarding influence on coumarin formation, the effect increasing progressively with the bulk of the alkyl group. β-Naphthol does not condense with α-ethyl-, α-propyl-, or α-isopropyl-aceto-acetates (38).

For groups other than alkyl, α-chloroacetoacetate has been studied to some extent. In addition to the usual phenols, it condenses with p-cresol, giving the corresponding 3-chlorocoumarin (172).

Ahmed and Desai (2) have systematically studied the formation of coumarins from phenols and cyclic β-ketonic esters. They find generally that the cyclic β-ketonic esters behave similarly to open-chain ones, the fused cyclo ring having an effect comparable to that of an α-methyl substituent.

Recently Shah and his coworkers (203, 209, 124) in a series of papers have systematically studied the Pechmann condensation of ethyl acetosuccinate, ethyl α-acetoglutarate, and ethyl α-(α-hydroxy-β,β,β-trichloroethyl)acetoacetate with a view to finding the effect of —CH$_2$COOC$_2$H$_5$, —CH$_2$CH$_2$COOC$_2$H$_5$, and —CH(OH)CCl$_3$ substituents in the α-position of the acetoacetic ester molecule on the course of the reaction. The results show that the behavior of the phenols with the above esters is similar to their reactivity with other β-ketonic esters. Ethyl acetosuccinate also gives coumarins in good yields with m-cresol and β-naphthol. In spite of the heavier bulk of its substituent, the acetosuccinate is as reactive as, or even more reactive than, the corresponding simple α-alkyl-acetoacetate. The introduction of a negative group like carbethoxyl in the alkyl group tends to increase the reactivity of the ester, a result which may be attributed to its greater enolization. Similar observations have also been made in the case of α-acetoglutarate, the next homolog of the acetosuccinate.

The substituent —CH(OH)CCl$_3$, considered in relation to a simple α-ethyl group in acetoacetic ester, appears to be more reactive, judging from the experimental results. The reaction in the case of resorcinol and similar phenols is completed within a shorter period: p-cresol condenses only at lower temperature; o- and m-cresols condense, though the reaction takes a different course. These observations are interesting, as the —CH(OH)CCl$_3$ group is a very heavy substituent compared to ethyl. The increased reactivity of ethyl α-(α-hydroxy-β,β,β-trichloroethyl)acetoacetate may be attributed to the presence of OH and CCl$_3$ groups in the alkyl chain.

While various α-substituted acetoacetates have been investigated, recently Kotwani, Sethna, and Advani (122, 123) have made a systematic attempt to study the reactivity of γ-substituted acetoacetic esters in the Pechmann condensation. They find that ethyl γ-phenylacetoacetate condenses with various phenols, giving 4-benzylcoumarins. The same authors, on condensing ethyl butyroacetate (ethyl γ-ethylacetoacetate), found that the γ-substituent has a considerable inhibiting effect and that in some cases it is even more inhibitory than the corresponding α-substituent or even a negative γ-substituent like the carbethoxyl group, as in ethyl acetonedicarboxylate, which may be regarded as ethyl γ-carbethoxyacetoacetate.

B. CONDENSING AGENTS

In the foregoing section, we have reviewed the work done on the effect of substituents in the phenolic nucleus as well as in the β-ketonic ester molecule. We shall now turn to the rôle of condensing agents in the course of the Pechmann reaction.

There are two possibilities in the reaction between a β-ketonic ester and a phenol, one giving rise to a coumarin derivative (A) and the other giving rise to a chromone derivative (B):
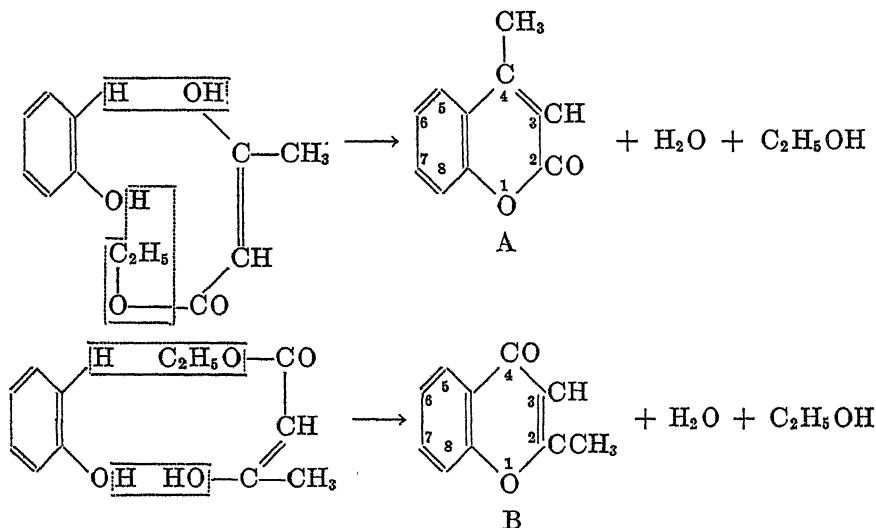
Phosphorus pentoxide and sulfuric acid as condensing agents

Simonis and his collaborators (212) condensed β-ketonic esters with phenols in the presence of phosphorus pentoxide instead of sulfuric acid, as used by Pechmann, and claimed to have obtained chromones instead of coumarins in all the cases. Jacobsen and Ghosh (110) claimed to have obtained chromones in some cases even when sulfuric acid was used as condensing agent. This work of Jacobsen and Ghosh has been contradicted by Baker (14) and by Baker and

Robinson (19). They definitely proved, by synthesizing chromones by unambiguous methods, that the so-called γ-pyrones or chromones of Jacobsen and Ghosh were really coumarins or 1,2-benzopyrones.

It would therefore appear that the condensation of phenols with ethyl acetoacetate and its substituted derivatives would lead to the formation of coumarins in the presence of sulfuric acid, whereas, with phosphorus pentoxide, chromones would be formed. To settle this point, the Simonis reaction has been the subject of extensive investigation by several workers.

In connection with their work on the benzoylation of ketones from phloroglucinol, Canter, Curd, and Robertson (32) thought of the procedure of the Simonis reaction as a convenient solution of the problem of independently synthesizing chromones for purposes of comparison. They found that the condensation of phloroglucinol and ethyl α-methylacetoacetate with phosphorus pentoxide as condensing agent proceeds readily but that it results in the formation of the coumarin derivative in place of the expected chromone. Furthermore, the dimethyl ether of phloroglucinol and the same ester in the presence of phosphorus pentoxide also gave the dimethyl ether of the above coumarin. In view of the unexpected behavior of phloroglucinol, they extended the reaction to resorcinol. Simonis and Remmert (214) had studied this condensation and assigned to the condensation product obtained the constitution 7-hydroxy-2,3-dimethyl-1,4-benzopyrone (I). Robertson and coworkers found that Simonis' so-called chromone was identical with 7-hydroxy-3,4-dimethylcoumarin (II).
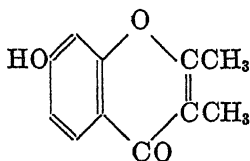
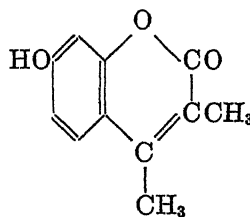I   II

Robertson and coworkers extended the investigation to other phenols with similar results; they found that resorcinol, phloroglucinol, pyrogallol (33), and α-naphthol (173) always gave coumarins, irrespective of the condensing agent used. Robertson and coworkers (175) studied different phenols with a view to investigating whether coumarins or chromones are formed in the presence of phosphorus pentoxide. They concluded that the Simonis reaction depends entirely on the nature of the phenol and is independent of the nature of the ester, a view which was modified by them later on.

Simultaneously, Chakravarti (37) also showed that resorcinol reacts with β-ketonic esters to form coumarins and not chromones, even in the presence of phosphorus pentoxide. He also studied the condensation of pyrogallol, phloroglucinol, m- and p-cresols, and α- and β-naphthols with various β-ketonic esters in the presence of both of the condensing agents and obtained results essentially similar to those of Robertson and coworkers.

Dey and Lakshminarayanam (68) supported the earlier view of Robertson by studying the condensation of β-naphthol and acetoacetic ester. They found that in the case of β-naphthol even sulfuric acid gives a mixture of coumarin and chromone. The statement, "Those phenols which readily give coumarins with β-ketonic esters in presence of sulphuric acid also give coumarins and not chromones in presence of phosphorus pentoxide; those phenols which give coumarins in poor yield or do not react at all, produce chromones with phosphorus pentoxide in good yield", has been supported by numerous experimental facts obtained by both Robertson and Chakravarti and their collaborators.

The following generalization can be made on this point:

(1) Sulfuric acid as a condensing agent always gives a coumarin derivative, provided the reaction takes place. There is, however, a remarkable exception to the above generalization in the case of β-naphthol, which gives a mixture of coumarin and chromone even in the presence of sulfuric acid. Recently, Adams and Mecorny (1a) have reported the exclusive formation of a chromone in the Pechmann condensation of ethyl acetoacetate with 4-chloro-3,5-dimethylphenol.

(2) Phenols which react readily in the presence of sulfuric acid, e.g., resorcinol, pyrogallol, orcinol, α-naphthol, etc., also give coumarins by the Simonis reaction, i.e., in the presence of phosphorus pentoxide.

(3) Phenols which do not form coumarins at all or form them in poor yields with sulfuric acid, give chromones by the Simonis reaction, i.e., in the presence of phosphorus pentoxide.

(4) β-Ketonic esters with an α-alkyl substituent favor chromone formation in the Simonis reaction, but the substituent if too heavy retards and inhibits the reaction. Negatively substituted esters give coumarins in good yield, but if the substituent is of a strongly negative character, it is eliminated.

(5) Phosphorus pentoxide is the only condensing agent which promotes chromone formation. This singular behavior of phosphorus pentoxide is noteworthy. It may be mentioned, however, that Robertson and Goodall (171) have recently shown that phosphoryl chloride acts like the pentoxide in the condensation of p-xylenol, giving rise to chromones identical with the respective chromones obtained by the phosphorus pentoxide method.

Some other condensing agents

Besides the two common condensing agents, several others have been used to a greater or less extent. Pechmann used anhydrous zinc chloride in some condensations. Carl Bülow (31) condensed resorcinol and other phenols with ethyl o-carboxyphthalylacetoacetate and ethyl o-carboxybenzylacetoacetate in the presence of dry hydrogen chloride in glacial acetic acid solution and obtained coumarin derivatives. Appel (9) introduced absolute alcohol in place of acetic acid as the solvent. Various acidic and basic agents, like phosphoric acid, sodium ethoxide, boric anhydride, and sodium acetate, have been tried by Chakravarti (39) in place of sulfuric acid. Horrii (107) has investigated the use of ferric chloride, stannic chloride, and titanium chloride.

Naik, Desai, and Trivedi (146) introduced the use of phosphoryl chloride as the condensing agent to condense α-naphthol with α-benzylacetoacetate, as

sulfuric acid fails in this case. It has also been found to be successful in effecting the condensation of resacetophenone and other 4-acylresorcinols (60, 61) with acetoacetic ester to give 7-hydroxy-6-acyl-4-methylcoumarins, sulfuric acid failing to bring about this condensation.

It has been found that the above condensing agents do not yield results of any particular value or interest, except in the case of phosphoryl chloride. In all cases coumarins are obtained, as with sulfuric acid, with some variations in the yields. Hydrogen chloride and phosphoric acid appear to be cleaner agents, as they do not produce highly colored and pasty products, but they have failed to promote the condensation where sulfuric acid has failed. Phosphoryl chloride, however, promises to be of interest, as already indicated above.

Anhydrous aluminum chloride as condensing agent

In exploring the use of other condensing agents, Sethna, Shah, and Shah (194) have in recent years introduced the use of a new condensing agent—namely, anhydrous aluminum chloride—which has proved to be of great value in the condensation of phenols with β-ketonic esters. The condensation is generally carried out in the presence of a solvent—anhydrous ether, in which aluminum chloride dissolves readily (206), or generally in dry nitrobenzene where elevated temperatures have to be used. The results obtained, which are unique in some respects, are outlined below:

(a) *Simple phenols*—The same coumarins are obtained as with sulfuric acid, in some cases with higher yields. In no case has a chromone been obtained. The reagent is of particular value in the case of slightly reactive monohydric phenols: phenol uniformly gives a yield of 30–40 per cent of 4-methylcoumarin (193), the recorded yield in the literature being 3 per cent; o-cresol, which does not condense in the presence of sulfuric acid, readily gives 4,8-dimethylcoumarin.

(b) *Phenolic esters*—Mention has already been made in another connection of the fact that methyl β-resorcylate condenses with acetoacetic ester in the presence of sulfuric acid, giving a 7-hydroxy-4-methylcoumarin-6-carboxylate. The
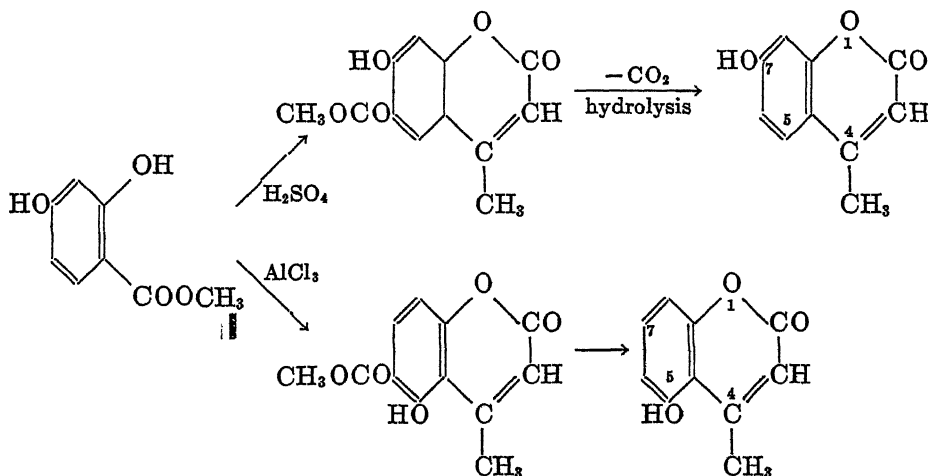
same condensation in the presence of aluminum chloride affords mainly the isomeric 5-hydroxycoumarin derivative (194), from which by hydrolysis and subsequent decarboxylation 5-hydroxy-4-methylcoumarin is readily obtained. Methyl 2,4-dihydroxy-5-ethylbenzoate (196) and methyl phloroglucinolcarboxylate (192) were also successfully condensed with acetoacetic ester in the presence of this condensing agent.

(c) *Phenolic ketones*—It has already been pointed out that resacetophenone does not condense with ethyl acetoacetate in the presence of sulfuric acid or sodium ethoxide. However, it readily undergoes the condensation in the presence of aluminum chloride, the product obtained in high yield being 5-hydroxy-6-acetyl-4-methylcoumarin (194). Orcacetophenone and 2,4-dihydroxybenzophenone react similarly, giving the corresponding 5-hydroxycoumarins. 2-Acetylresorcinol gives 7-hydroxy-8-acetyl-4-methylcoumarin in better yield than with sulfuric acid. *o*-Hydroxyacetophenone, quinacetophenone, and gallacetophenone do not condense (204). Shah and coworkers (47, 56) have extended the reaction to several 4-acylresorcinols and have obtained 5-hydroxy-6-acylcoumarins which are almost inaccessible by the hitherto known methods.

Desai and Hamid (61) were able to condense resacetophenone and other 4-acylresorcinols, using phosphoryl chloride as the condensing agent. 7-Hydroxy-6-acylcoumarins were obtained.
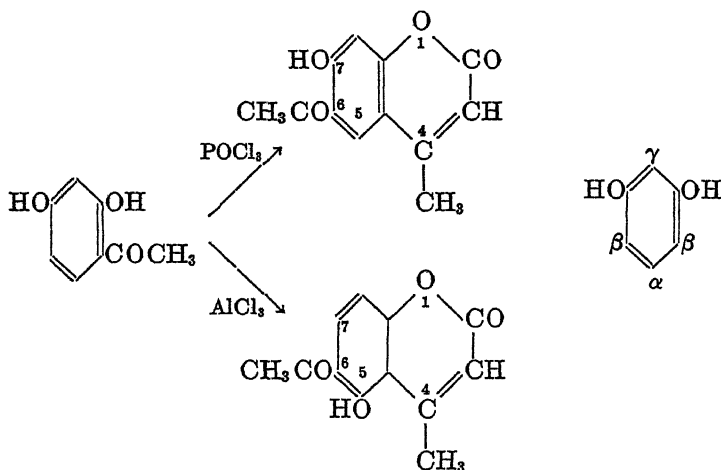
A reference has been made earlier to the fact that Chakravarti (41, 43) condensed 4-nitroresorcinol with acetoacetic ester, using sulfuric acid as condensing agent, and obtained 7-hydroxy-6-nitro-4-methylcoumarin. The same condensation with aluminum chloride was carried out by Parekh and Shah (150), who obtained 5-hydroxy-6-nitro-4-methylcoumarin.

Deliwala and Shah (57) condensed various substituted resacetophenones with acetoacetic ester in the presence of aluminum chloride and found that the presence of negative groups like —NO$_2$, —COOCH$_3$ and —COCH$_3$ in the resacetophenone nucleus has a deactivating effect and therefore prevents the condensation, while positive groups like —C$_2$H$_5$ have no such effect, the reaction readily taking

place. They (58) have also studied the condensation of resacetophenone with ethyl α-alkylacetoacetates. A negative substituent in the α-position has a completely inhibitory effect on the reaction. A positive substituent has less inhibitory effect, but as the bulk of the substituent increases, the reactivity diminishes; thus, ethyl α-propylacetoacetate did not condense. It may be mentioned here that resacetophenone could not be condensed even with ethyl α-methylacetoacetate with phosphoryl chloride as condensing agent. Thus the introduction of an α-alkyl substituent is not so inhibitive if aluminum chloride is used.

The striking feature of aluminum chloride as the condensing agent lies in the fact that, whereas other condensing agents give 7-hydroxycoumarins from resorcinol derivatives, this reagent modifies the course of the reaction with the production of 5-hydroxycoumarins, the condensation taking place in the usually inaccessible γ-position of the resorcinol nucleus.

The above results indicate that if the β-position in the resorcinol molecule is occupied by groups like carbethoxyl, carboxyl, acyl, benzoyl, and nitro, then the product obtained depends upon the condensing agent used.

5-Hydroxycoumarin, which cannot be obtained by the aluminum chloride method, has been synthesized by Shah and Shah (199) from methyl 2-hydroxy-3-formyl-4-methoxybenzoate by its Knoevenagel condensation with ethyl malonate and subsequent hydrolysis, followed by decarboxylation and demethylation of ethyl 5-methoxy-8-carbomethoxycoumarin-3-carboxylate.

Several substituted 5-hydroxycoumarin derivates have been synthesized by Shah and his coworkers (200, 207) from 3-formylhydroxyphenyl ketones by the application of the Knoevenagel method, the formyl ketones being easily obtained by them through their modified Gattermann reaction.
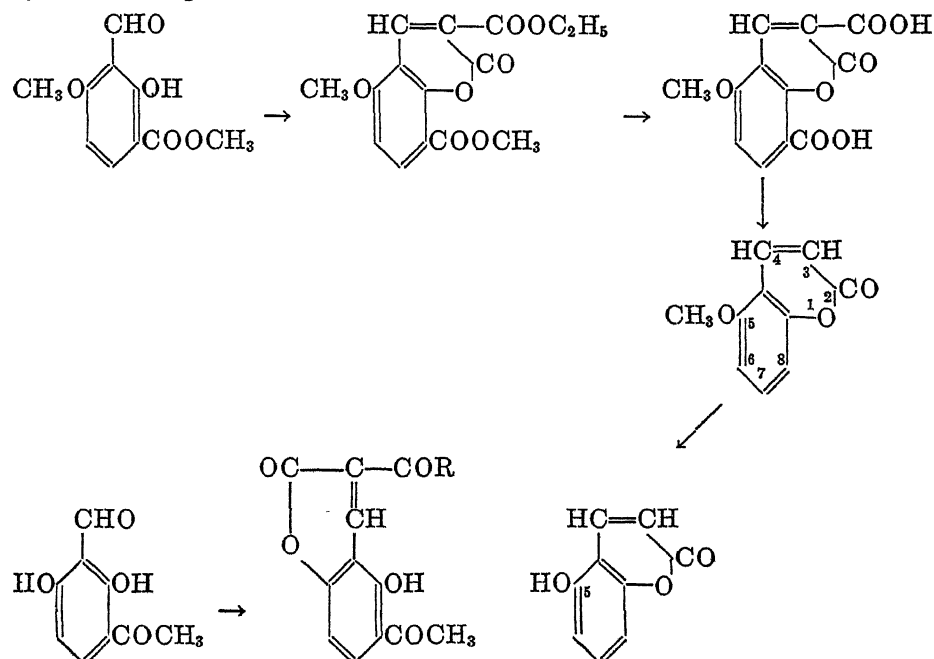
IV. MECHANISM OF REACTION BETWEEN β-KETONIC ESTERS AND PHENOLS

Two different views have been advanced with regard to the mechanism of coumarin formation by the Pechmann reaction. Robertson and coworkers (175) conclude from experimental evidence that cinnamic acid is formed as an intermediate.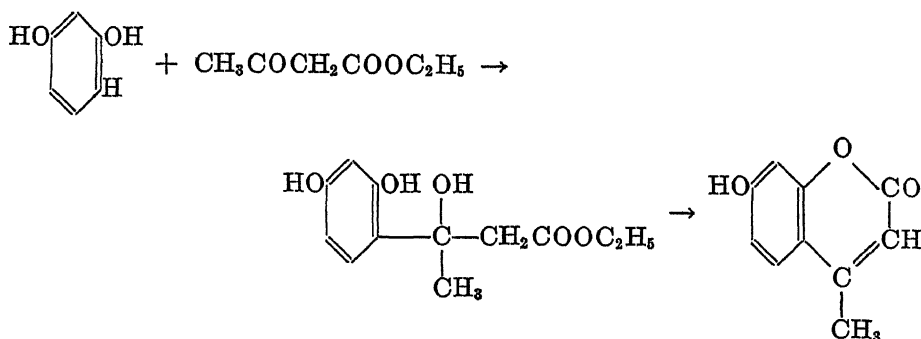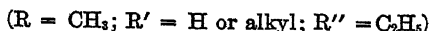 They observed that 2-methoxy-β,4-dimethylcinnamic acid was converted into 4,7-dimethylcoumarin by 86 per cent sulfuric acid and, further, that m-tolyl methyl ether and o,o-dimethylresorcinol gave rise to 4,7-dimethylcoumarin and 7-methoxy-4-methylcoumarin, respectively.

Ahmed and Desai (3) offer the explanation that the reactive hydrogen of phenol coördinates readily with the carbonyl group of the β-ketonic ester. This hydrogen is in the ortho position to the hydroxyl group and should be sufficiently reactive; otherwise, the tendency for the formation of the additive product will be little or nil.

$$\text{HO—}\underset{\text{H}}{\bigodot}\text{—OH} + CH_3COCH_2COOC_2H_5 \rightarrow$$

$$\text{HO—}\bigodot\text{—}\underset{\overset{|}{CH_3}}{\overset{OH}{\underset{|}{C}}}\text{—}\underset{|}{CH_2COOC_2H_5} \rightarrow \text{coumarin structure}$$

The additive product then undergoes dehydration and cyclization to coumarin. The substituent in the β-ketonic ester will facilitate or retard the formation of the additive product, and the effect will be partly polar and partly steric.

With regard to the mechanism of the Simonis reaction, Robertson and collaborators consider that the first stage in the reaction is the formation of the phenoxy acid (or its ester) by the interaction of the enolic form of the ester and phenol with the removal of elements of water, the phenoxy compound then undergoing ring closure with the formation of chromone.

$$\bigodot\text{—OH} + \underset{\overset{|}{COOR''}}{\overset{HO—C—R}{\overset{\|}{C—R'}}} \longrightarrow \underset{\overset{|}{COOR''}}{\overset{O—C—R}{\overset{\|}{C—R'}}} \longrightarrow \text{chromone structure}$$

(R = CH₃; R' = H or alkyl; R'' = C₂H₅)
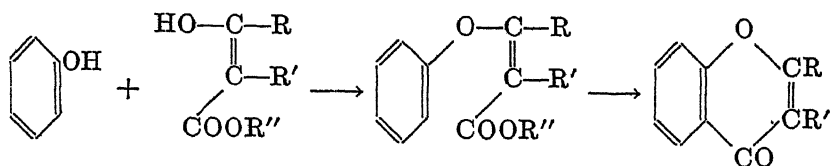
In support of this mechanism, Robertson and collaborators cite as evidence the synthesis of 1,4-pyrones from phenoxyfumaric acid and from β-phenoxycinnamic acids by Ruhemann and coworkers (177).

Ahmed and Desai consider that, since only those phenols which do not contain a reactive hydrogen ortho to the hydroxyl group give chromones by the Simonis reaction, the reactive hydrogen belongs to the hydroxyl group, which interacts

with β-ketonic esters giving rise to aryl esters of these acids (I). These aryl esters then undergo an isomeric change analogous to the Fries migration, forming o-hydroxybenzoylacetylmethane (II), which is dehydrated to the chromone derivative (III).
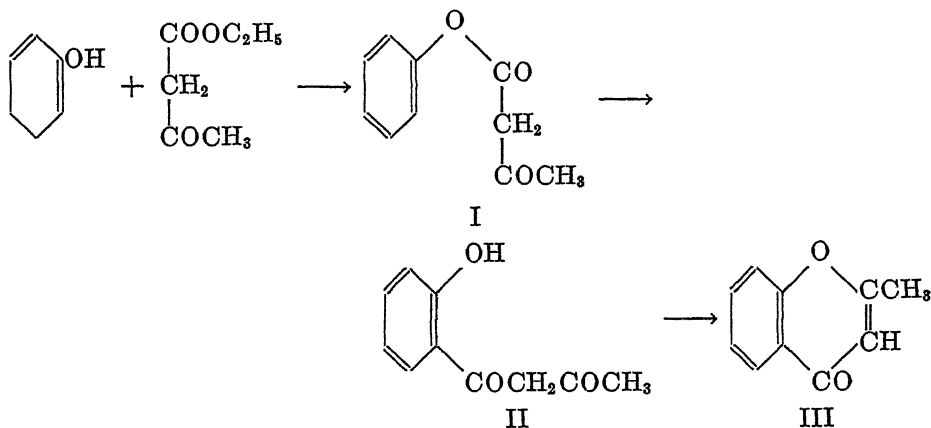
The specific condensing action of phosphorus pentoxide, according to Ahmed and Desai, is to facilitate the formation of I or II or both, as the conversion of II into III may be accomplished with the help of any dehydrating agent. The intermediate formation of diketone (II) in the Kostanecki acylation has been proved by Baker (15). Ahmed and Desai consider that it is also produced in the course of the Simonis reaction.

Of the two essentially similar views described above regarding coumarin formation, that of Robertson and coworkers is simpler and appears more plausible than that of Ahmed and Desai, whose assumption of additive compound formation, though ingenious, is not based on any experimental evidence. With regard to chromone formation, the two views are fundamentally different. Robertson and coworkers assume the condensation of phenolic hydroxyl with acetoacetate, the point of attack being the =C(OH)— part of the ketonic ester. Ahmed and Desai assume the condensation of phenolic hydroxyl with the carbethoxyl group of the ester, with the elimination of an alcohol molecule. This is not very likely, as the —C(OH)= group is usually more reactive than —C$_2$H$_5$ in the acetoacetic ester molecule. Ahmed and Desai further assume the transformation to be analogous to the Fries migration in the presence of phosphorus pentoxide, which has been quite recently found by Schönberg and Mustafa (180) to be effective in the Fries reaction on phenolic esters. No definite opinion is possible till further evidence is forthcoming.

The formation of 5-hydroxycoumarin derivatives in the condensation of res-acetophenone, methyl β-resorcylate, etc., with aluminum chloride as condensing agent, obviously depends upon the reactivity in the 2-position in the resorcinol nucleus. Resorcinol derivatives easily undergo various substitutions and condensations in the 4-position in preference to the 2-position, which is usually inaccessible.

$$HO \underset{3}{\overset{2}{\bigcirc}} OH$$
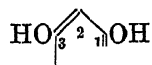
The reactivity in the 2-position in the present case becomes explicable in the light of the view that in these o-hydroxyacyl ketones one of the Kekulé forms becomes stabilized, owing to chelation between hydroxyl and acyl groups which requires the fixation of double bonds in the benzene nucleus between the carbon atoms bearing these two groups. Such a view of fixation of double bonds in the benzene nucleus was first put forward by Mills and Nixon (142) for compounds in which another ring is fused on to the benzene ring, and has been applied by Baker and his collaborators (16, 18) to substitution in resorcinol derivatives.

The formation of 5-hydroxycoumarins in the present case also depends upon the stabilization of one of the Kekulé forms by the fixation of double bonds. Thus, for example, in resacetophenone, owing to the existence of a chelate bond between the hydroxyl and acetyl groups, the double bonds are fixed and the point of attack is the carbon atom joined by a double bond to that bearing the other hydroxyl group; the condensation therefore takes place here, with subsequent ring closure to give 5-hydroxy-6-acetyl-4-methylcoumarin.
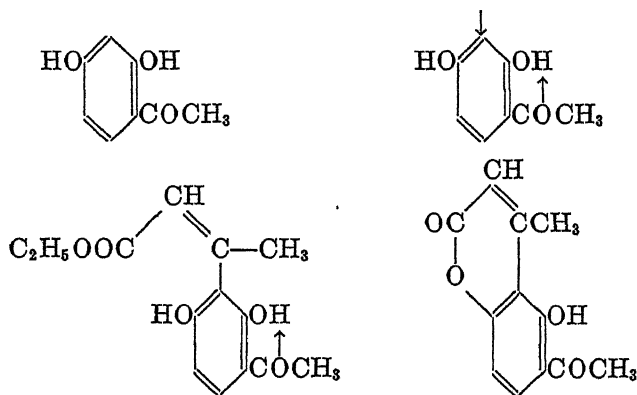
The non-condensation of gallacetophenone can also be satisfactorily explained by the application of the above views. It will be seen that the carbon atom marked with an asterisk, where the condensation may be expected to take place,
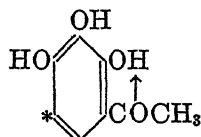
is not reactive, as it is united by a single bond to the carbon atom bearing the hydroxyl group. Baker states that aluminum chloride may prevent the chelation, but since 5-hydroxycoumarins are exclusively formed in good yields, it appears that this reagent does not prevent chelation and may even promote it.

This view also finds support in the work of Shah and Shah (200) on the formylation of 4-acylresorcinols, wherein it is found that the formyl group also enters the γ-position.

The formation of 5-hydroxycoumarins from methyl β-resorcylate and 4-nitroresorcinol in the presence of aluminum chloride can also be similarly explained. Two points bearing on the mechanism require to be mentioned. Whereas, in the case of resacetophenone and other 4-acylresorcinols, it is generally accepted that chelation between OH and —COR groups requires the double bond bearing these groups to be fixed, in the case of β-resorcylic acid and its ester, no definite conclusion seems to have been arrived at, as no case of 3-substitution in these compounds was previously known. Again, Baker is of the opinion that the presence of aluminum chloride must prevent chelation, owing to the formation of an addition product. However, in the present case it appears that aluminum chloride has a specially favorable action in promoting chelation, as other condensing agents produce 7-hydroxycoumarin derivatives. The view advanced above that the γ-position in methyl β-resorcylate is activated by the fixation of double bonds finds support in the work of Shah and Laiwalla (207), who found that the formyl group can be conveniently introduced in the γ-position in methyl β-resorcylate by the use of aluminum chloride in the Gattermann reaction.

V. METHODS FOR DISTINGUISHING COUMARINS AND CHROMONES

Much of the confusion that prevailed following the work of Simonis was due to the absence of any definite method by which a coumarin or chromone could be identified. At present, however, a number of methods are available. These can be divided into two groups: (1) those based upon the hydrolysis of the compound by alkaline reagents, and (2) those based upon the preparation of some special derivative. Earlier workers mainly depended upon hydrolytic methods, which often led to erroneous conclusions. The initial action of alkali on a coumarin is to open the pyrone ring, with the formation of a salt of coumarinic acid which on acidification regenerates the original coumarin. Although coumarinic or *cis-o*-hydroxycinnamic acids are as a class unstable, there are a few exceptions of moderately stable coumarinic acids, such as those derived from 8-nitrocoumarin (141), 3-acetyl-4,5,7-trimethylcoumarin-6,8-dicarboxylic ester (113), 6-nitro-αβ-1,2-naphthopyrone, and 6-nitro-αβ-1,2-naphthopyrone-4-acetic acid (64), and a few others. It will be noticed that, in all these cases, the coumarinic acid is stabilized by the entrance of acidic groups, the effect being more marked when the acidic radical is in position 8 of the coumarin ring system. Dey and Krishnamurthi (66) devised a method of separating a mixture of 6-nitro- and 8-nitro-coumarins by taking advantage of the superior stability of the coumarinic acid formed from the latter.

The entrance of alkyl groups, on the other hand, is found to produce the opposite effect. However, Dey, Rao, and Sankaranarayanan (71) have found certain βα-1,2-naphthopyrone derivatives which give stable coumarinic acids, notwithstanding the presence of alkyl groups and the absence of any acidic substituent in the coumarin ring.

If the action of alkali is prolonged under suitable conditions, the stable coumaric acid is formed (85, 88). Sometimes the action of alkali results in the complete elimination of the pyrone ring, leading to the formation of a phenol (267, 128) or a styrene derivative (153).

Limaye and Kulkarni (133) have exhaustively studied the effect of substituents in 7-hydroxycoumarin on the elimination of the pyrone ring by caustic alkali.

In the case of chromone, according to Simonis (211), the hydrolysis occurs in two stages: the β-diketone is first formed and breaks up to yield either an o-hydroxy acid or an o-hydroxy ketone; the acid may further decompose giving a phenol.

What type of splitting a chromone will undergo will depend upon the nature of the chromone and of the hydrolyzing agent and the conditions of the hydrolysis, or both. The action of sodium ethoxide on chromones generally leads to the acid type of splitting (268).

Information concerning a substance supposed to be a coumarin or a chromone may be obtained by consideration of the product of its hydrolysis: (*i*) If an o-hydroxy diketone is obtained, the substance is definitely a chromone. (*ii*) If a coumaric acid is obtained, the substance is definitely a coumarin. Some exceptions, however, have been recorded where the hydrolysis takes an abnormal course: 7-hydroxy-4,5-dimethylcoumarin (198) and 4-isopropyl-1,2-α-naphthopyrone (5) have been found to give orcacetophenone and 1-hydroxy-2-naphthoic acid, respectively, on hydrolysis. (*iii*) If an o-hydroxy ketone or o-hydroxy acid is obtained, the substance must be a chromone. Exceptions have been known, such as those mentioned above. (*iv*) If a phenol is obtained, no definite conclusion can be drawn. It must be made clear that negative results in any of the above cases do not indicate the absence of a coumarin or chromone.

The results have to be carefully considered if the confusion arising out of the wrong interpretations, as happened in the case of Jacobsen and Ghosh, is to be avoided.

Canter and Robertson (34) have devised an elegant method for the identification of coumarins. It consists in hydrolyzing the coumarin and preventing the closure of the lactone ring by subsequent methylation by dimethyl sulfate to get an o-methoxycinnamic acid derivative. The formation of the o-methoxycinnamic acid is a sure indication that the substance is a coumarin derivative. This method has been modified by Shah and Shah (205), who found that by dissolving the substance in acetone and then adding dimethyl sulfate and finally alkali, the formation of the methoxycinnamic acid was rendered more facile; in several cases where the Robertson method fails the modified method was found satisfactory.

An elegant method for distinguishing 2-methylchromones is due to Heilbron and coworkers (99), who from considerations of valency showed that the methyl group in the 2-position of a chromone should be reactive. This was realized experimentally, as 2-methylchromones condense with aromatic aldehydes in the presence of sodium ethoxide, giving styrene derivatives. Several workers, notably Chakravarti (42) and Robertson (119), have used styrene formation as a characteristic reaction of 2-methylchromones. Coumarins do not give styrene derivatives.
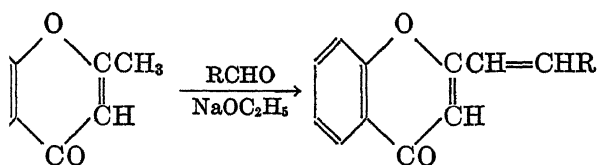

It has been observed that 2-methylchromones with certain substituents, e.g., —OCH$_3$, —OCOCH$_3$, —OCH$_2$C$_6$H$_5$, etc., in the 5- and 7-positions, as well as 3-acylated chromones, do not yield styrene derivatives (93, 132). Hence no definite conclusion can be drawn from a negative result in this test.

In the Kostanecki acylation of o-hydroxy ketones, the formation of a 3-acyl derivative is taken to be indicative of chromone formation. In view of the recent work of Sethna and Shah (197) on the Kostanecki–Robinson acylation of orcacetophenone, where 4-acylcoumarins have been obtained, the production of an acylpyrone as a criterion of chromone formation may be regarded with some doubt.

Lastly, mention may be made of Wittig's method (268) of separating a mixture of coumarin and chromone. The mixture is treated with sodium ethoxide; on acidification the coumarin is regenerated, but the β-diketone is unaffected and can be extracted with alkali, from which the chromone can be obtained. This method has been utilized by Heilbron and coworkers in several cases. Its success depends on two factors: (i) the absence of hydroxycoumarins and (ii) the fact that the chromone ring opens on treatment with sodium ethoxide and is not closed again on acidification along with the coumarin ring.

Desai (59) has evolved a diagnostic test for coumarins and chromones. When a glacial acetic acid solution of bromine is added to a solution of coumarin or chromone in the same solvent, the former gives invariably the soluble 3-bromo derivative, while the latter gives an insoluble perdibromide from which the original chromone is regenerated by treatment with sulfurous acid solution. If the chromone contains a hydroxyl group, the action of bromine gives a bromo-chromone.
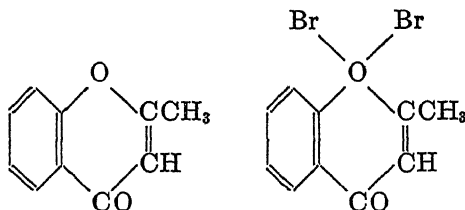
VI. Substitution in the Coumarin Ring System

The coumarin ring system, which comprises a benzenoid part and the heterocyclic α-pyrone part, can give several derivatives with substituents in either component of the ring system. This can be realized either by condensing substituted phenols with different β-ketonic esters—as already discussed under the synthetic methods—or by substitution in the simple coumarin derivatives. The latter work is discussed in this section.

Several halogen, nitro, amino, and sulfonic acid derivatives have been obtained. There are, however, many difficulties in the preparation of alcohols, aldehydes, ketones, and carboxylic acids of the coumarin series. It may be mentioned that the benzene nucleus of the coumarin ring system is not so reactive as that of a simple benzene derivative.

Acyl- and formyl-coumarins

With a view to the preparation of acetylcoumarins, Desai and Hamid (61) tried the Friedel–Crafts reaction on 7-hydroxy- and 7-methoxy-4-methylcoumarins but it proved unsuccessful. However, the synthesis of hydroxyacetylcoumarins was realized by Limaye (130), by applying the Fries migration to 7-acetoxy-4-methylcoumarin with the help of anhydrous aluminum chloride, a process which resulted in the formation of 7-hydroxy-8-acetyl-4-methylcoumarin in quantity, along with a small amount of 7-hydroxy-6-acetyl-4-methylcoumarin. The Fries migration of acyloxy- or aroyloxy-coumarins to yield the acyl- or aroyl-hydroxycoumarins has been studied by various workers. Several 7-hydroxy- as well as 5-hydroxy-6-acylcoumarins have been directly synthesized by the condensation of resacetophenone and other 4-acylresorcinols with acetoacetic ester in the presence of either phosphoryl chloride (61) or aluminum chloride (194). Similarly, carboxylic acids of the coumarin series have been synthesized.

The Gattermann reaction on coumarins is unsuccessful, but Späth and Pailer (242) were able to introduce the formyl group in 7-hydroxycoumarin by means of hexamethylenetetramine, the 8-aldehydrocoumarin being obtained in poor yield. Rangaswamy and Seshadri (166) prepared aldehydohydroxy-coumarins,

-chromones, and -flavones by the same method. Sen and Chakravarti (185) prepared 6-aldehydocoumarin.

Nitration

Clayton (50) observed that coumarin was found to resist strongly the introduction of more than one nitro group, but this resistance diminishes very appreciably with the introduction of alkyl groups in the molecule: he found that when 8-nitrocoumarin is nitrated, the second nitro group goes to the 6-position, and that when 6-nitrocoumarin is nitrated, 3,6-dinitrocoumarin is obtained. The presence of a nitro group in the 3-position is shown by the reaction with alkali. When the substance is boiled with alkali, preferably concentrated ammonia solution, it dissolves and on subsequent acidification yields the corresponding salicylaldehyde derivative. This remarkably easy rupture of the lactone ring is found to be a property of all 3-nitrocoumarins. Clayton studied the nitration of various substituted coumarins and from the results concluded that there can be no doubt that the difficulty of obtaining higher nitration products of coumarin is due to the general acidity conferred on the molecule by the lactone ring; the introduction of methyl groups gradually weakens this acidity and makes the molecule more susceptible to the action of nitric acid.

Pechmann and Obermiller (158) investigated the nitration of 7-hydroxy-4-methylcoumarin and its methyl ether. They obtained 8- and 6-nitro compounds, respectively. This is in agreement with the similar reactivity exhibited by the same coumarin in other reactions: e.g., the formation of 8-aldehydo and 8-acyl compounds, the formation of angular α-pyrones, and the transformation of 7-allyloxycoumarin to 7-hydroxy-8-allylcoumarin.

The nitration of coumarin was found to proceed in the first place with exclusive substitution in the 6-position. Dey and Krishnamurti (66) revealed the formation also of small quantities of 8-nitrocoumarin in the process. The nitration of coumarin by benzoyl nitrate gives 5-nitrocoumarin in quantitative yield (83).

Fries and Lindemann (86) nitrated 8-chloro- and 8-bromo-7-hydroxy-4-methylcoumarins and obtained 8-chloro-6-nitro- and 8-bromo-3,6(or 5,6)-dinitro-7-hydroxy-4-methylcoumarins, respectively.

Dey and Kutti (67) have investigated the nitration of 8-methoxy- and 8-hydroxy-coumarins and obtained 8-methoxy-5-nitrocoumarin and 8-hydroxy-7-nitrocoumarin, respectively. Thus hydroxyl and methoxyl groups direct the nitro groups to different positions.

Recently, Parekh and Shah (149) have studied the nitration of 5-hydroxy-4-methylcoumarin and 5-hydroxy-4-methylcoumarin-6-carboxylic acid and its methyl ester. The nitration of the coumarin at lower temperature gave the 8-nitro derivative and at higher temperature the 6,8-dinitro derivative, while the acid and its ester afforded 8-nitro derivatives.

Halogenation

In the halogenation of coumarins, the halogen atom enters the pyrone ring initially in the 3-position and then enters the benzene nucleus. Thus, Simonis

and his coworkers (213, 215) found that the bromination of 4-methylcoumarin gave 3-bromo-4-methylcoumarin. By the action of bromine in carbon disulfide solution in a sealed tube, 3,6-dibromo-4-methylcoumarin was obtained, and 3,6,8-tribromo-4-methylcoumarin resulted when the reaction was carried out under pressure. In the case of hydroxycoumarins, bromination is not restricted to the pyrone ring alone but proceeds to the benzene ring as well (223). This difficulty is overcome by protecting the hydroxyl group by acetylation (115), methylation, or carbethoxylation (87). The presence of an acyl group in the benzene ring in the position ortho to the hydroxyl group seems to have a similar effect. For example, the bromination of 6-acetyl-5-hydroxy-4-methylcoumarin yields the monobromo derivative mixed with the dibromo derivative. To get a good yield of the 3-bromo derivative only, the bromination of the acetyl derivative was carried out, the deacetylation taking place during the reaction. Dey and Kutti (67) have found that in the halogenation of 8-methoxycoumarin, in contrast to the usual rule of halogen entering the pyrone ring first, halogenation proceeds with substitution in the benzene ring. In the bromination of 4-methyl-daphnetin, Sakai and Kato (178) obtained 3-bromo- and 3,4-dibromo-4-methyl-daphnetins.
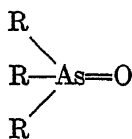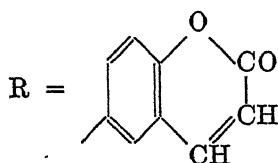
In the halogenation of coumarin-4-acetic acids, Dey and Radhabai (70) observed that the methylene group in the side chain in the 4-position was attacked and that 4-halogenocoumarinacetic acids were obtained. Addition of the halogen to the double bond of the pyrone ring was observed in the case of $\beta\alpha$-1,2-naphthopyrone-4-acetic acid only.
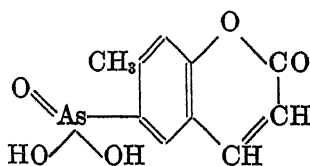
Sulfonation

Perkin (161) carried out the sulfonation of coumarin but did not establish the constitutions of the products obtained. Sen and Chakravarti (183) have sulfonated coumarin and 6-nitrocoumarin and obtained coumarin-6-sulfonic acid, coumarin-3,6-disulfonic acid, and 6-nitrocoumarin-3-sulfonic acid, the constitutions of which were proved by oxidation of the pyrone ring with alkaline potassium permanganate to yield the known salicylic acid derivatives.

Arsonation

Goswami and Das-Gupta (92) made the first attempts to introduce arsenic into the coumarin ring system. By applying Bart's reaction to 6-aminocoumarin, they obtained tricoumarylarsenic oxide (I). The reaction was extended to other coumarin derivatives, which yielded only mono derivatives (II).
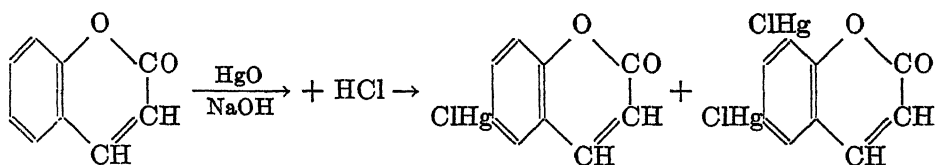
Mercuration

Sen and Chakravarti (184) were successful in introducing mercury into coumarins. They found that the usual reagents effectively employed in the mercuration of organic compounds failed to mercurate coumarin in aqueous, alcoholic, or acetic acid solution. When, however, the lactone ring was broken open and the masked hydroxyl group brought to prominence, mercuration readily took place with mercuric oxide or with mercuric acetate. By boiling the dilute solution of coumarin in alkali with yellow mercuric oxide, monochloro- and dichloro-mercuricoumarins were obtained. If the 6-position was occupied, no mercury compound was formed but geometrical inversion to o-coumaric acid derivatives took place.

Mercuration by mercuric acetate in alkaline solution gave diacetoxymercuric derivatives.

Naik and Patel (147) have studied the effect of substituents in the mercuration of coumarins. Ahmed and Desai (2) have mercurated coumarins obtained from cyclic β-ketonic esters, using the method of Sen and Chakravarti. The coumarins from resorcinol, orcinol, and phloroglucinol gave diacetoxymercuro derivatives. The coumarins from α-naphthol did not undergo mercuration.

Seshadri and Rao (190) have investigated the reaction of mercury salts on coumarins. They found that mercuric acetate in methyl alcoholic solution reacts with the double bond of the coumarin and further mercurates the benzene ring if the 6- and 8-positions are free, giving 3,6,8-triacetoxymercuro-4-methoxy-melilotic anhydride:
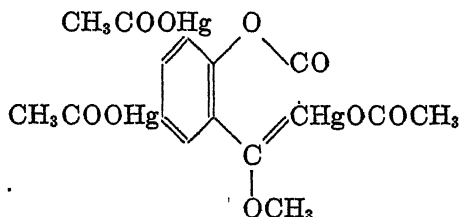

Mercuric chloride also adds to the double bond of coumarin and of 7-methylcoumarin.

Geometrical inversion in the acids derived from coumarins

Coumarins, being the lactones of o-hydroxycinnamic acids, give on treatment with alkali the salts of the corresponding coumarinic acids, which on acidification immediately revert to the coumarins; therefore the coumarinic acids are the

cis compounds. They are incapable of free existence, though some stable *cis* acids are known (page 23). If the action of alkali is prolonged under suitable conditions, *cis*-to-*trans* inversion takes place.
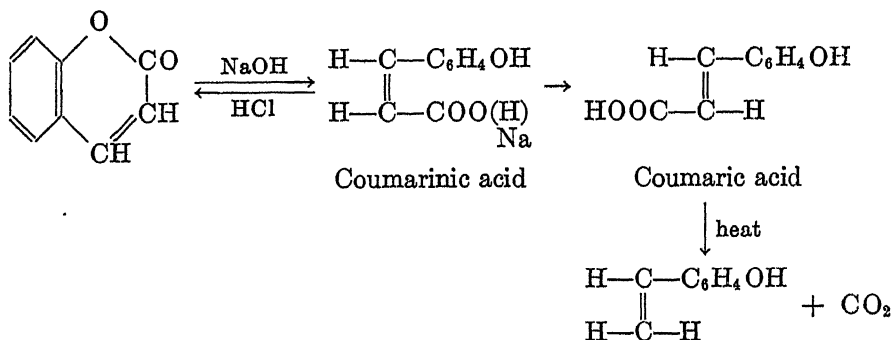
In this reaction, the initial formation of the alkali salt of coumarinic acid takes place, which then undergoes inversion under the influence of the reagent. This change is greatly facilitated by the addition of some reagent which acts as an addendum at the double bond of the pyrone ring. Methods have been devised in which substances like sodium hydrogen sulfite (74, 79) or mercury compounds (187) have been successfully employed to effect the inversion to the *trans* isomer.

The *trans* acids—coumaric acids—are capable of free existence and on heating decompose into carbon dioxide and hydroxystyrenes (72, 78). They undergo inversion to the *cis* forms under the influence of sunlight and are then readily converted into coumarins, the esters inverting even more readily than the free acids.

Among other methods of producing the *trans*-to-*cis* change, concentrated sulfuric acid at 100°C. has been sometimes used. Seshadri and Rao (191) found that this method gives only a poor yield; a saturated solution of hydrogen chloride in alcohol was superior to sulfuric acid in some cases. They have shown that a satisfactory method of *trans*-to-*cis* inversion is to boil the *trans* isomer with mercuric chloride solution.

VII. SYNTHETIC USES OF COUMARINS

Coumarin and its derivatives are substances of much potential value for synthetic purposes. Their easy accessibility opens the way through suitable reactions to the synthetic preparation of various other heterocyclic compounds, such as coumarones, furanocoumarins (or furocoumarins), chromono-α-pyrones, flavono-α-pyrones, and chromenes, as well as natural products containing such ring systems.

Coumarones

3-Halogenated coumarins are converted into the corresponding coumarilic acids by treatment with alkali. The pyrone ring opens and loses a molecule of halogen acid, with the subsequent formation of coumarilic acid, which on

heating breaks down into carbon dioxide and yields coumarone. This is known as Fittig and Ebert's reaction.
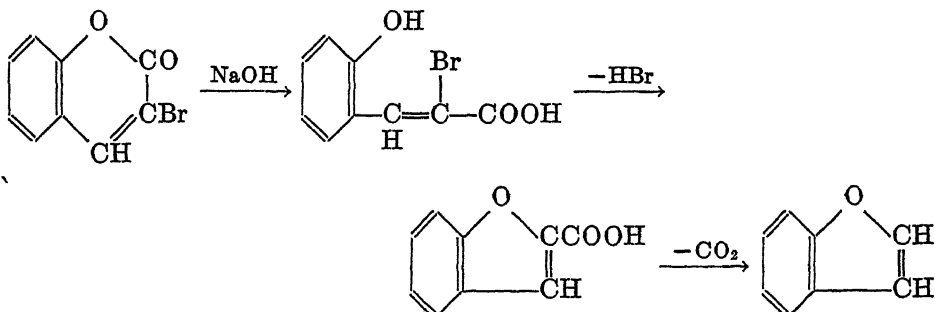
This method, which works well with simple coumarins, is not directly applicable to hydroxycoumarins, as bromination of these coumarins is not restricted to the pyrone ring but proceeds to the benzene ring; hence, bromo-free coumarones are not obtained. This difficulty is overcome by protecting the hydroxyl group and carrying out the bromination to get the monobromo derivative.

Thus, coumarone is a degradation product of coumarin in which the five-membered ring is obtained from the pyrone ring. Several coumarones have been prepared from coumarins in this way. Coumarones are used in industry for the manufacture of coumarone resins.

Furanocoumarins (or furocoumarins)

If the furan ring is built on a suitably substituted coumarin or chromone derivative, it leads to the synthesis of coumaronocoumarins or coumarono-chromones, generally known as furanocoumarins or furanochromones. Alternatively, one can start with an appropriate coumarone and build up the α-pyrone or γ-pyrone ring, leading to the same furanocoumarins or furanochromones. Depending upon the position of the furano ring, several isomeric forms of furano-coumarins are possible: for instance,
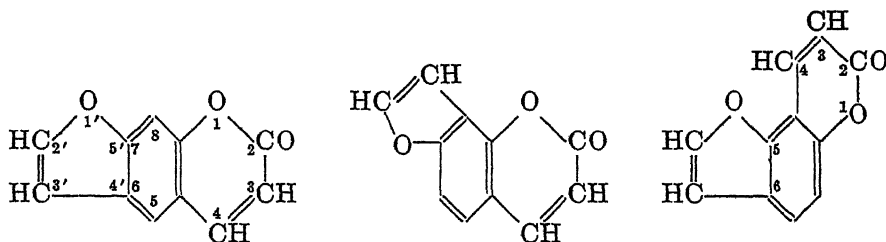
The above three types are theoretically derivable from resorcinol.

In recent years, several furanocoumarins have been synthesized by Limaye (130) and his coworkers (131) by treating the dry sodium salt of an o-acyl-hydroxycoumarin or the coumarin in sodium ethoxide with bromoacetic ester; the resulting O-acetate (I) was hydrolyzed and the O-acetic acid (II) cyclized to the furan ring by treatment with acetic anhydride.

I

II

(R = H or alkyl)
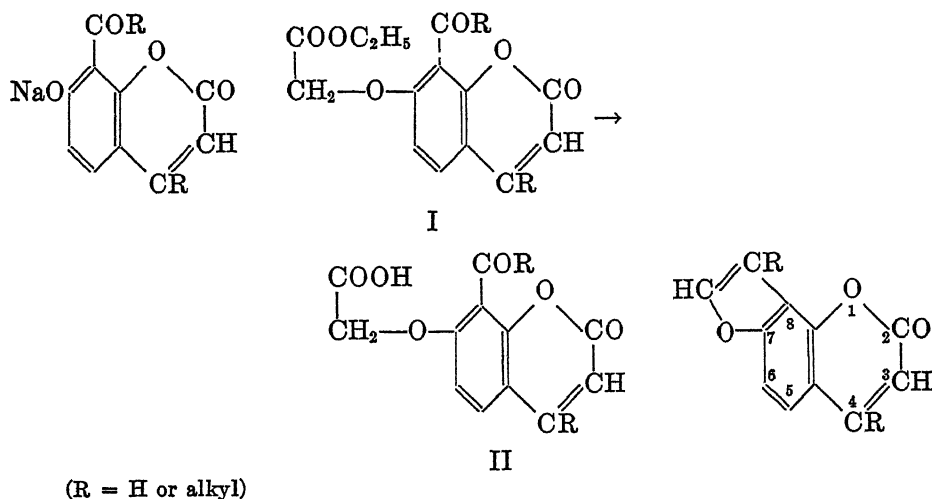
An o-hydroxyacylcoumarin required for this synthesis is easily available by the Fries migration of acyloxycoumarins. Späth and Pailer (242) substituted bromoacetic ester by bromoacetal, while Ray, Silooja, and Vaid (170) used chloroacetone or bromoacetone in alkaline solution in the above condensation and cyclized the resulting product.

The above synthesis from 7-hydroxy-8-acylcoumarins leads to the formation of the furan ring between the 7- and 8-positions of the coumarin ring; such furano-coumarins are known as the angular type of furanocoumarins. If the ring is between the 6- and 7-positions of the coumarin, it will be the linear type, as obtained by Ray et al. All the types of these furanocoumarins shown above have been synthesized.

Shah and Shah (201) synthesized unsubstituted furanocoumarins from 5-hydroxycoumarin derivatives. In this case the sodium salt method was found unsatisfactory; hence the bromoacetic ester was condensed in dry acetone solution in the presence of potassium carbonate. This modification has been found to be satisfactory, and several furanocoumarins from 6-acyl-5-hydroxy-4-methyl-coumarins have been synthesized by Chudgar and Shah (unpublished work).

Coumarino- and chromono-α-pyrones

Hantzsch and Zurcher (95) condensed a few umbelliferones with malic acid in the presence of sulfuric acid and obtained the first representatives of the coumarino-α-pyrones in poor yield. They did not prove their constitutions. Sen and Chakravarti (186) prepared some other members of the same class. Rangaswami and Seshadri (166) showed that when umbelliferone is condensed with malic acid, two isomeric compounds are formed: angular coumarino-7,8-α-pyrone (I; R = H) is the major product; the second compound, obtained in small quantity, is taken to be the linear compound, coumarino-7,6-α-pyrone (II; R = H). Under the same conditions, 4-methylumbelliferone gives only one coumarino-α-pyrone, viz., 4-methylcoumarino-7,8-α-pyrone. 4-Methyl-

umbelliferone and ethyl acetoacetate also give 4,4'-dimethylcoumarino-7,8-α-pyrone (I; R = CH₃), which is obtained in good yield when resorcinol is condensed with an excess of the ester in the presence of alcoholic hydrochloric acid. Coumarino-α-pyrones are prepared by the Perkin reaction on o-hydroxyformyl-coumarins, which are obtainable with difficulty.

Another way of synthesizing these compounds is to subject an o-hydroxyacyl- or aroyl-coumarin derivative to the Kostanecki acylation. This will give either chromono-α-pyrones or coumarino-α-pyrones. Shah and coworkers (194, 204, 56) have synthesized several of these types of compounds from 6-acyl-5-hydroxy-coumarins.

I   II

Chromono-α-pyrone
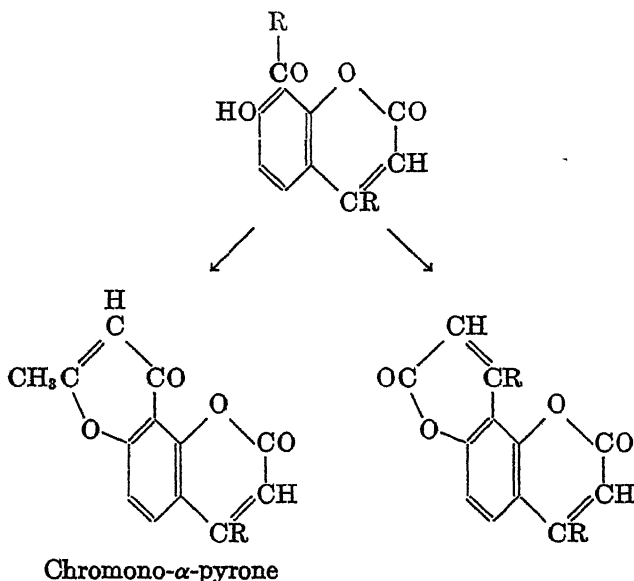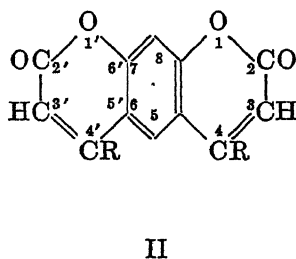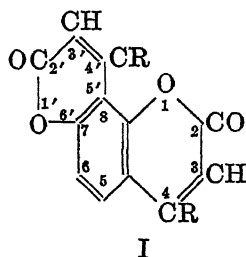
2-Acylresorcinols

The introduction of an acyl or aroyl group into the γ-position of the resorcinol nucleus was difficult until Limaye (128, 129) developed an elegant method for this synthesis. Starting with a 7-hydroxycoumarin derivative, its acyloxy or aroyloxy compound is prepared, which on Fries migration gives mainly an 8-acyl-7-hydroxycoumarin derivative, from which the pyrone ring is eliminated

by boiling with aqueous alkali, the resulting product being a 2-acyl- or 2-aroyl-resorcinol. This method, named the Nidhone process by the author, has been extensively applied for the preparation of various 2-acyl- and 2-aroyl-resorcinols.

(R′ = acyl or aroyl; R = H or alkyl)
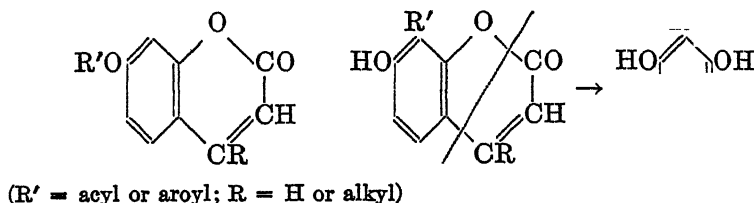
Action of Grignard reagents on coumarins

When Grignard reagents react with dihydrocoumarins, carbinols (I) are obtained which on ring closure give 2,2-dialkylchromans (221).

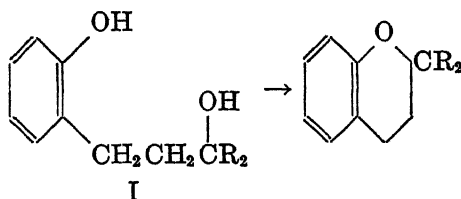The action of Grignard reagents on coumarins, however, is much more complicated because of the presence of the conjugated double bonds, and a variety of products is obtained depending upon the conditions of the reaction. Decker and Fellenburg (54, 55) have shown that the interaction of coumarin and Grignard reagents under carefully specified conditions leads to the production of monoalkyl pyrylium salts. Willstätter and his coworkers (266) have used this reaction for the synthesis of anthocyanidins from 3-methoxycoumarins.

Houben (108), Löwenbein, Pongráez, and Spiess (136), and Shriner and Sharp (210a) have recorded a number of investigations leading to the formation of substituted chromenes and have suggested a mechanism for the course of the reaction employing a large excess of the Grignard reagent.

Heilbron and Hill (104, 105) investigated the action of Grignard reagents on substituted coumarins with the object of synthesizing flavylium chlorides containing methoxyl and hydroxyl groups in the 4-position, compounds of the latter type being expected to lose hydrogen chloride and pass into flavones. They obtained only diaryl products. A detailed investigation of 3- and 4-substituted coumarins led to the conclusion that the production of either a Δ^2- or a Δ^3-chromene is influenced solely by the position of the substituent in the pyran ring. They also found that when dilute solutions under the conditions employed by Willstätter are used with 3-methyl-, 3-phenyl-, and 3-methoxycoumarins, the reaction proceeds smoothly and gives good yields of the corresponding 2-phenylbenzopyrylium salts, but that when more concentrated solutions are employed, Δ^3-chromenes are obtained.
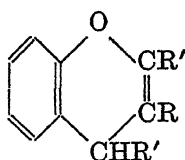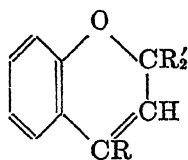
2,4-Diaryl-Δ^2-chromene   2,2-Diaryl-Δ^3-chromene

The formation of 2,2-dialkyl- and 2,2-diaryl-Δ^3-chromenes, directly or through the isolation of the intermediate unsaturated carbinols, has been utilized by many workers (26, 30, 137) for the synthesis of such derivatives. The formation of chromonols in the reaction between Grignard reagents and coumarins has also been noted.

Kartha and Menon (116) have studied the condensation of methoxymethyl-umbelliferone with an excess of Grignard reagents: α-naphthocoumarin has been condensed with phenylmagnesium bromide. All the condensation products are assigned the Δ^3-chromene structure, in conformity with the general conclusions of Heilbron: i.e., when the 4-position is occupied by a substituent, the product is the Δ^3-compound.

Other reactions

Row and Seshadri (176) synthesized coumarino-7,8-furanones by the Fries reaction on the chloroacetoxy derivatives of 7-hydroxycoumarins.

Two molecular equivalents of 4-hydroxycoumarin condense with formaldehyde, giving 3,3'-methylenebis(4-hydroxycoumarin), the causative agent of the hemorrhagic sweet clover disease of cattle. The reaction has been extended to other aliphatic and aromatic aldehydes (250); the products obtained have been dehydrated to form the substituted 1,4-pyran derivatives, 3,3'-alkylidene- or 3,3'-arylidene-4,4'-epoxydicoumarins, by means of acetic anhydride in pyridine.
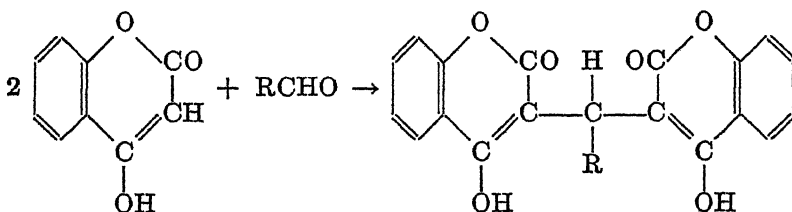
Adams and coworkers (1) added 2,3-dimethylbutadiene to coumarin and some substituted cinnamic acids. With coumarin they obtained 8,9-dimethyl-6a,7,10,10a-tetrahydrodibenzopyrone in poor yield. *trans-o*-Hydroxycinnamic acid added the same diene more readily to give the same pyrone.
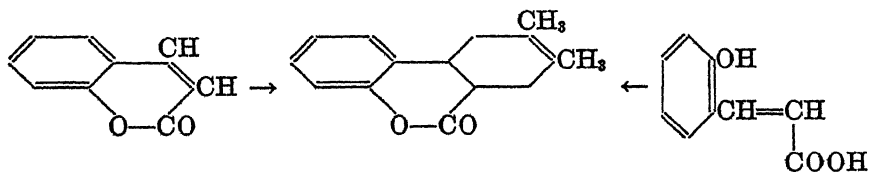
Furocoumarones (dicoumarones) have been synthesized by Hanztsch (96), Algar and coworkers (4), and recently by Limaye and Panse (134).
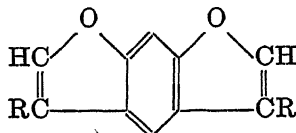
Limaye and Sathe (135) have described a synthesis of some members of the furanochromone class by building up a furan ring on a suitably substituted chromone derivative. The other possibility of synthesizing the γ-pyrone ring on a suitable coumarone derivative has not yet been realized. The synthesis of the hydroxyacylcoumarone required as the starting material is being attempted.

Recently Shah (202) synthesized coumarinochalcones from 6-acetyl-5-hydroxy-4-methylcoumarin. Though a considerable amount of work has been published on chalcones, this appears to be the first instance of the formation of chalcones from heterocyclic ketone derivatives.
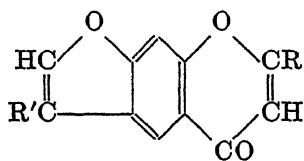
Furanochromones
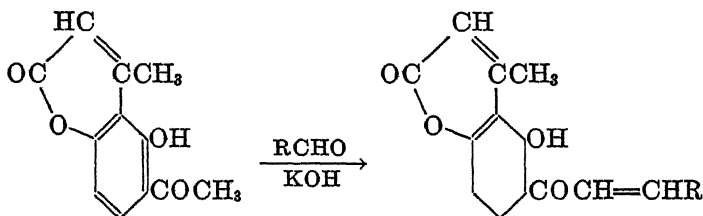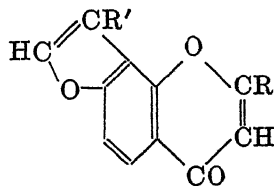
By applying the Doebner–Miller reaction to 6-aminocoumarin and 6-amino-4-methyl-α-naphthopyrone, Dey, Sarkar, and Seshadri (75) have synthesized a class of 2-methylquinolino-6,5-α-pyrones; the simple quinolino-α-pyrones have been obtained by Dey and Goswami (65) by the application of the Skraup reaction.
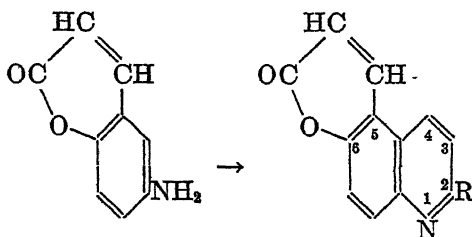
(R = H or CH₃)

Widman (265) has prepared a new type of coumarin in which a cyclopropane ring forms a part of the nucleus by condensing 3-acetylcoumarin with ω-chloro-benzophenone in cold alcoholic solution.
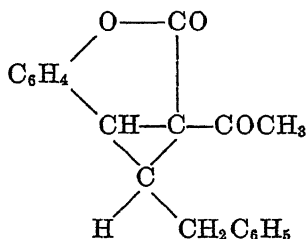
VIII. PHYSICOCHEMICAL AND OTHER PROPERTIES OF COUMARINS

Tasaki (253) investigated the absorption spectra of several coumarin derivatives in 0.001 M alcoholic solution for wave numbers (λ^{-1} in centimeters) from 2000 to 5000. Coumarin shows two absorption maxima in this region, at 3200 Å. and 3600 A. When hydroxyl groups are introduced, the substance shows only one absorption maximum.

E. Rakower (164) has described and discussed the spectra of methyl 3-cinnamoylacetylcoumarin-7-carboxylate, dicinnamoylmethane, and coumarin.

The fluorescence and absorption spectra of 7-hydroxycoumarin-3-carboxylic acid and methyl 7-hydroxy- and 7,8-dihydroxy-coumarin-3-acetates have been investigated by Czapska-Narkiewiez (52). The fluorescence maxima are at 4596, 4727, and 4679 Å. and the absorption maxima are at 3300, 4314, and 4517 Å., respectively.

The Raman spectra of coumarin in the solid state as well as in solution in different solvents have been examined by Seshadri (188) with reference to (1) the C═C and (2) the C═O frequencies. Of the three frequencies belonging to (1), which are fairly constant throughout, the two lower ones represent the aromatic double bonds of the benzene ring and the third represents the ethylene double bond of the pyrone ring. The C═O frequency is considerably low in the solid state as well as in the solutions with certain polar solvents, possibly owing to the weakening of the C═O bond by the formation of hydrogen bonds through coördination. Mookerjee and Gupta (143) have also investigated the Raman spectra of some coumarin derivatives and chromone in the solid state and in solution with reference to shifts in C═O frequency.

The dipole moment of coumarin at 20°C. (4.51 × 10^{-19} E.S.U.) has been measured and indicates a state of resonance between the normal and excited states (169).

The crystal structure of coumarin has been investigated by Ramaswamy (165). An exhaustive study of the structural influences governing the fluorescence exhibited by coumarin derivatives has been made by Seshadri and coworkers (20, 167, 168). They have studied several hydroxycoumarins as well as chromones with respect to their fluorescence. A number of umbelliferone derivatives with different substituents in the 3-position have also been examined in this respect. The presence of carbethoxyl, carbonyl, or acetyl in the 3-position of

7-hydroxy- and 7-methoxy-coumarins enhances the fluorescent property of the compounds to such an extent that they exhibit bright fluorescence even in neutral alcoholic solutions, whereas the same groups in the 4-position produce no such effect. 7-Hydroxycoumarins produce bright fluorescence in neutral or alkaline media, but the intensity is considerably diminished in acid media. The fluorescence of 7-hydroxycoumarins is blue, whereas their methoxy derivatives show fluorescence more on the violet side. 3-Benzoyl compounds are yellow in the solid state as well as in solution and exhibit no visible fluorescence under any conditions.

Dihydroumbelliferone and its derivatives in which there is no ethylenic double bond do not give fluorescence. 5-Hydroxycoumarins dissolve in alkali with a deep yellow non-fluorescent color.

The possibility of resonance as the result of electron mobility is now recognized as the essential cause of absorption, and this may also be considered as one of the deciding factors for fluorescence emission. The results are explained on this basis.

A large amount of work has been done on the reactivity of the double bonds in coumarins. The unsaturated center in coumarins seems to differ greatly in reactivity from the double bond in related compounds. The double bond between carbon atoms 3 and 4 in the coumarin nucleus is highly reactive; it adds bromine (162), hydrogen cyanide, and sodium bisulfite with great facility. Seshadri (189, 190) investigated this reactivity of the double bonds in coumarins in comparison with α,β-unsaturated carbonyl compounds, and found that coumarin condensed easily with cyanoacetamide and yielded I, which on hydrolysis gave the acids II and III, the latter being converted into II.
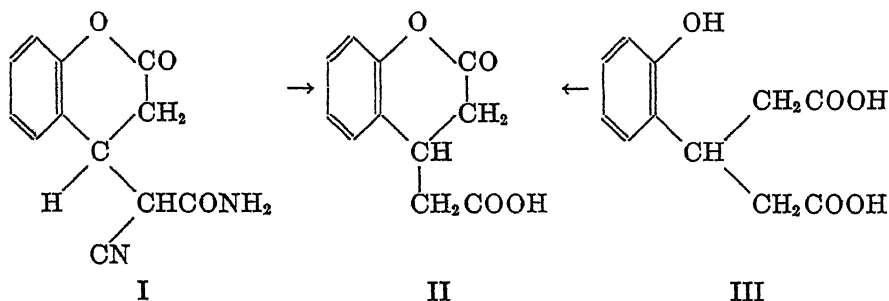
Dey and Rao (73), as well as Dodge (79), found that sodium hydrogen sulfite reacts with coumarin to give a β-sulfonic acid, which on being boiled with concentrated caustic potash solution gives o-coumaric acid. This reaction furnishes a convenient method of converting coumarins into their coumaric acids.
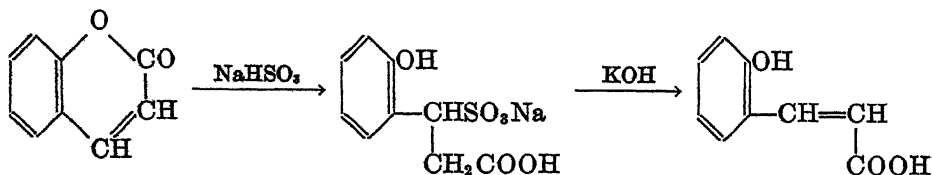
Coumarin-3- and 4-acetic acids comprise within their molecules a double bond between carbon atoms 3 and 4 in the pyrone ring and a reactive methylene group attached to either of these atoms. Dey and Row (74) and Dey and Seshadri (77) have shown that coumarin-4-acetic acids resemble malonic acid in decomposing smoothly and quantitatively into 4-methylcoumarins and carbon dioxide. Further, coumarin-4-acetic acids and their esters readily condense with aromatic aldehydes both by Perkin's and by Knoevenagel's methods, giving rise to 4-coumarylphenylethylene and 4,3-dicoumaryl derivatives. Coumarin-3-acetic acids, on the other hand, are more stable and do not decompose even on heating at high temperatures; they are less reactive, as they do not undergo the Knoevenagel reaction.

Dey and Radhabai (70) have studied the action of halogens on the above acids. They found that halogen does not attack the double bond in the pyrone ring, as usually happens, but substitutes one of the methylene hydrogen atoms, a considerable amount of decarboxylation taking place. $\beta\alpha$-1,2-Naphthopyrone-4-acetic acid forms a solitary exception to the above generalization.
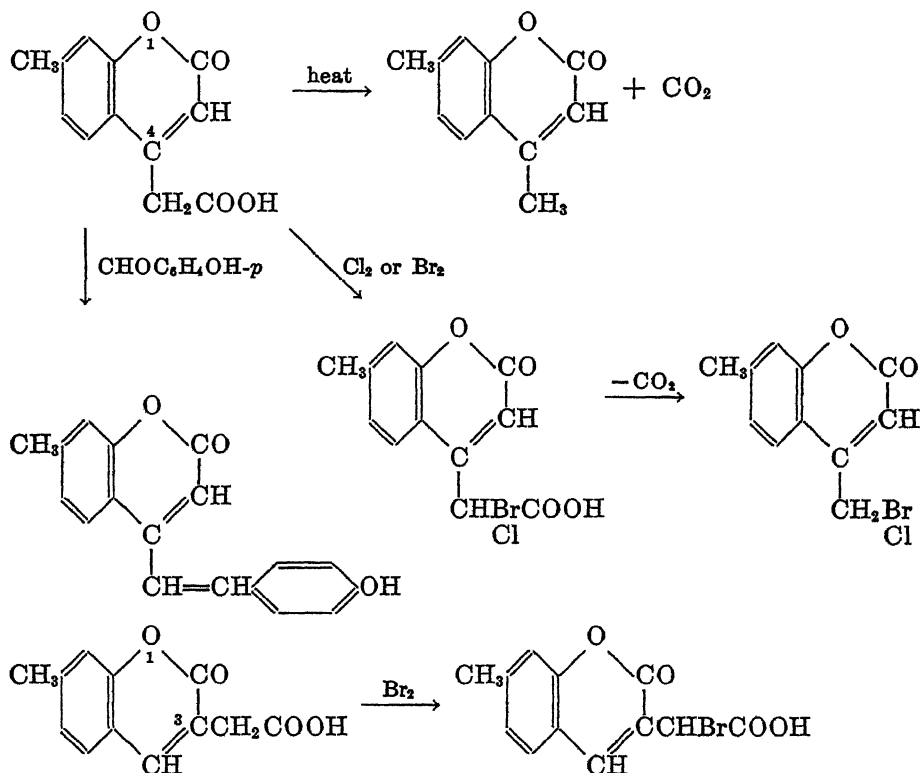
The hydrogenation of some substituted coumarins has been investigated with a view to obtaining information regarding the mechanism of formation of chroman derivatives (25a).

IX. NATURAL COUMARINS

Coumarins either in the free or in the combined condition are found to occur in different parts of the plant. The coumarin-bearing part, after suitable preliminary treatment, is extracted with a solvent and the extract is then subjected to various processes for isolation.

Isolation

A simple coumarin having no interfering group in the molecule and not in combination with glucose as glucoside can be isolated on treatment with dilute aqueous alkali solution (0.5 per cent). This treatment removes acids and other phenolic substances present in the extract. It is then treated with 5 per cent aqueous alkali alcoholic solution (caustic potash) for some time. By this treatment the coumarins are transformed into the potassium salts of the corresponding coumarinic acids as the lactone ring opens. Other reactions also occur simultaneously, e.g., any fatty material present is saponified. The mixture is then diluted with water and extracted with ether, whereby other substances (if any) are removed. The alkaline layer is then acidified; the acidic substances (if any) and coumarins are liberated. This mixture is taken up with an excess of ether and treated dropwise with dilute aqueous alkali; the acids dissolve and the coumarins remain behind. This process is repeated, whereby the acids along with a fraction of the coumarin are removed. Further separation is effected by vacuum distillation and/or sublimation. The coumarin is then purified by crystallization, chromatographic analysis, or other suitable method.

If the original plant material contained any hydroxycoumarins, they are carried down in the aqueous portion by initial treatment with aqueous alkali. That fraction is worked up; it is acidified, and extracted with ether, and separated from other fatty substances by extraction with petroleum ether. It is then distilled in a high vacuum and further purified by crystallization. To ascertain the presence of hydroxycoumarin, a portion of the liquid after acidifying is treated with diazomethane and then subjected to the treatment described above. If a methoxycoumarin is found to be present, a hydroxycoumarin was present in the original material. It may be mentioned here that prolonged treatment with alkali should be avoided, as it brings about the change of hydroxycoumarin into coumaric acid to a small extent.

Esters of hydroxycoumarins, if present, are found along with non-hydroxylic coumarins, but they may suffer in the course of separation on account of hydrolysis. Hydroxycoumarins are produced and separated along with them; they are to be worked out as described above.

Coumarin glucosides are detected thus: the soluble fraction after the treatment with alcoholic alkali is freed from impurities by extraction with ether; the glucoside is then decomposed by treating with dilute sulfuric acid, and the resulting aglucone is tested for coumarin. A quantitative estimation of simple coumarins is of possible interest in the scheme of separation of coumarins (114).

Classification

The coumarins isolated from plants and so far investigated can be grouped as shown below:

1. Coumarin and its simple derivatives.
2. Hydroxy- and methoxy(alkoxy)-coumarins and their glucosides. The hydroxy or alkoxy group may be present in the benzene or the pyrone ring.
3. Hydroxy- or methoxy-coumarins with an alkyl group in any part of the ring system.
4. Furanocoumarins (furan ring fused to benzene ring) with (i) an unsubstituted furan ring and (ii) a substituted furan ring.
5. Coumarins with a 2,2-dimethyl-1,2-chromene ring.

Several natural coumarins are so diversely substituted that they may be classified under more than one of the above subgroups. In such a case, the coumarin should be placed in that group which emphasizes a prominent point with regard to its constitution. The above classification is not final and will have to be modified or altered as our knowledge of the chemistry of natural coumarins advances.

At present about fifty natural coumarins are known and their chemical constitutions established. Thanks to Späth and coworkers, the natural coumarins have been extensively studied in recent years, and interest has been created in the subject.

Structure and occurrence

We shall now consider some reactions which have been used to prove the structure of natural coumarins.

Let us first consider coumarins having no acidic groups such as hydroxyl. A simple proof is that these non-hydroxylic coumarins are difficultly soluble in water and do not dissolve in alkali immediately, but when kept for a long time or when heated, dissolve completely with a yellow color, the corresponding alkali salt of the coumarinic acid being formed: if carbon dioxide is now passed into the alkaline solution or the solution is acidified, the acid is set free and, being unstable, immediately changes into a coumarin.

The transformation of coumarinic acid formed by the opening of the pyrone ring into coumaric acid—the *trans* isomer of coumarinic acid—is characteristic of the presence of the coumarin structure. The *trans* isomer can be changed into the *cis* form by the action of light or treatment with acids; the experimental realization of these isomeric changes is in many cases beset with difficulties.

| Coumarin | Coumarinic acid | Coumaric acid |
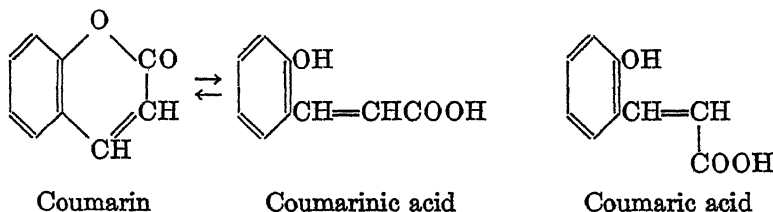
To decide whether a compound is a coumarin or not, hydrogenation is helpful. If a coumarin is present, one can introduce two hydrogen atoms into the coumarin structure by catalytic hydrogenation with palladium black or animal

charcoal. The resulting hydrocoumarin (I) is then changed into its hydroxy acid (II) by opening the lactone ring; the acid has no tendency to form the ring

II   I
Melilotic acid   Dihydrocoumarin
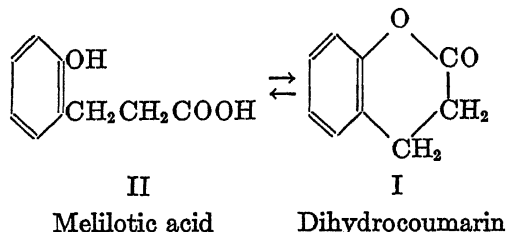
at ordinary temperature, in contrast to the hydroxycinnamic acids which easily change into coumarins. The hydrocoumarinic acids can be isolated in their free condition and converted into hydrocoumarins by distilling in a vacuum at higher temperatures.

The hydrocoumarin or hydrocoumarinic acid, on treatment with oxidizing agents such as nitric acid and potassium permanganate, gives succinic acid, which arises from the hydrogenated pyrone ring. This reaction is easily carried out, but it may be mentioned here that succinic acid can also arise from the side chain if any; therefore the above important reaction should always be considered in relation to other results. Dihydrocoumarins are dehydrogenated to coumarins in very good yield by the method of Späth and Galinovsky (230).

By the action of dimethyl sulfate on an alkaline solution of a coumarin, a methoxycinnamic acid is obtained. This method is a good one for distinguishing a coumarin structure, as stated previously.

An important method for determining the structure of a coumarin is to convert it into a benzene derivative of unambiguous constitution by cautiously oxidizing the o-methoxycinnamic acid. Hydroxycoumarins yield complicated results; on methylation, the disturbing factors are suppressed.

Glucosides of coumarins must first of all be hydrolyzed by dilute acids, and the resulting aglucones treated as described above.

With regard to the position of the hydroxyl group in the benzene nucleus of the coumarin, it has been found that in several cases, by fusion with potash, the heterocyclic ring and the side chain, if any, are split off and the simple phenol is obtained. By the action of nitric acid on a coumarin derived from resorcinol, styphnic acid, $C_6H(OH)_2(NO_2)_3$, is obtained; the methoxycoumarins on oxidation yield methoxybenzoic acids. A clue to the position of the group in the coumarin nucleus is thus obtained. In the case of a polyhydroxy coumarin, only an unambiguous synthesis can settle the constitution. Bargellini (24) has made an interesting observation that coumarins on oxidation with potassium persulfate are hydroxylated in the 6-position.

The number of double bonds can be easily estimated by quantitative hydrogenation, which has nowadays been developed even on a micro scale. As a rule, a coumarin double bond in the 3- and 4-positions is always more difficultly hydrogenated than a double bond in an unsaturated aliphatic side chain.

The structure and position of a side chain can be ascertained by the investi-

gation of oxidation products from the hydrogenated coumarins; an aliphatic carboxylic acid is obtained. The carbon atom of the carboxyl group comes from the nucleus; the other carbon atoms are from the hydrogenated side chain. The position of double bonds in the side chain is indicated by examining the oxidation products of the coumarin: aldehydes, ketones, and acids with a different number of carbon atoms are produced. All these reactions are illustrated below:

$$(CH_3)_2C{=}CHCH_2CH_2COCH_3$$

6-Methyl-5-hepten-2-one

Ostruthin

$$(CH_3)_2CHCH_2CH_2CH_2CHCH_2CH_2COOH$$
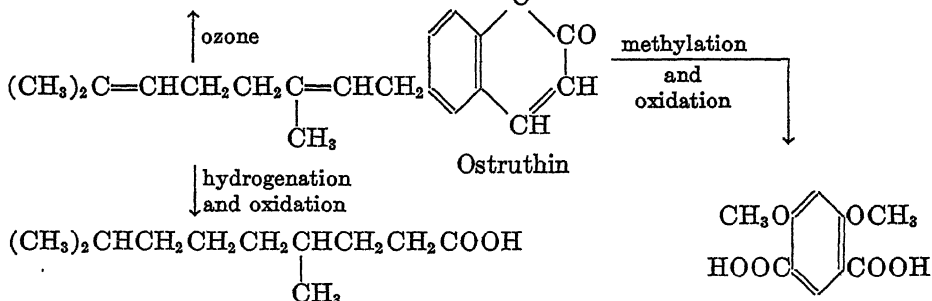
The presence of an unsubstituted furan ring is also determined by the oxidation of a furanocoumarin in alkaline solution, the furandicarboxylic acid being obtained.

Ethers of hydroxycoumarins and unsaturated alcohols containing the chain —$OCH_2CH{=}C(CH_3)_2$ undergo decomposition into their phenolic and alcoholic constituents by the action of glacial acetic acid to which a few drops of sulfuric acid have been added; the products can then be easily investigated.

We shall now briefly consider some natural coumarins.

The long-known sources of coumarin are the tonka bean, white clover, woodruff (*Asperula odorata*), etc. It is widely distributed in the plant kingdom and is found to be present in over sixty plants belonging to about twenty-four natural orders. It is often found as a glucoside or as a derivative of melilotic acid. Melilotoside is a crystalline glucoside of coumaric acid.

Out of the simple monohydroxycoumarins having the hydroxyl group in the benzene nucleus, only 7-hydroxycoumarin (called umbelliferone) has been long known. 5-, 6-, or 8-hydroxy-coumarins have not yet been found in plants. 7-Hydroxycoumarin was called umbelliferone, as it was obtained by the dry distillation of umbelliferous resin. It also occurs in the free condition in several plants. Various derivatives of umbelliferone are extensively distributed in the plant kingdom and await investigation.

Dihydroxycoumarins in which both the hydroxyl groups are in the benzene nucleus, as well as their glucosides, are frequently found in plants. The hydroxyl groups are in the 5,7-, 6,7- and 7,8-positions. Of the two hydroxyl groups, the one in position 7 generally takes part in the formation of glucosides or ethers. This has been found to hold good even in complex coumarins. 5,6-, 5,8-, and 6,8-dihydroxycoumarins have not yet been found to occur in nature.

5,7-Dimethoxycoumarin, known as citropten or limettin, is present in citron oil and similar essential oils.

Esculetin (or aesculetin) was known as a product of the decomposition of the glucoside esculin. This coumarin has also been found to occur in the free condition in the bark of horse chestnut and other plants. The constitution 6,7-dihydroxycoumarin is assigned to it. The esculin isolated from the horse chestnut is 6-β-glucosidoesculetin, while cichoriin, an isomeric glucoside of esculetin present in the leaves of the chicory plant, is its 7-glucoside.

Scopoletin, or 7-hydroxy-6-methoxycoumarin (97), occurs in its free form as well as in the form of its glucoside, scopolin, in belladonna and other plants.
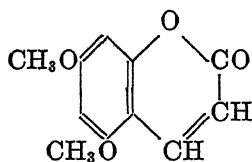
Citropten (limettin)
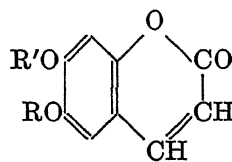
Aesculetin (R = R' = H)
Aesculin (R = $C_6H_{11}O_5$; R' = H)
Cichoriin (R = H; R' = $C_6H_{11}O_5$)

Scopoletin (R = H)
Scopolin (R = $C_6H_{11}O_5$)
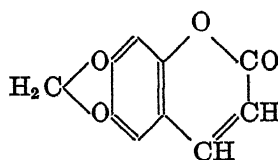
Ayapin

Ayapin, found in the leaves of *Eupatorium ayapana* Vent., is the methylene ether of esculetin and is the first instance of a methylenedioxycoumarin found in nature (226). Daphnetin, 7,8-dihydroxycoumarin, occurs in the form of its glucoside, daphnin, found in the plants of the Thymelaeceae order.

As a trihydroxycoumarin, fraxetin has been known since 1857. It was obtained from its glucoside fraxin, which is present in various species of ashwood. Its constitution has been proved to be 7,8-dihydroxy-6-methoxycoumarin (263). The glucose molecule in fraxin is combined with the hydroxyl group in the 8-position.
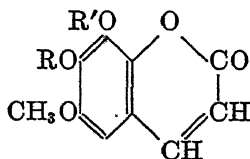
Fraxetin (R = R' = H)
Fraxidin (R = CH_3 :R' = H)
Isofraxidin (R = H; R' = CH_3)
Fraxin (R = H; R' = $C_6H_{11}O_5$)
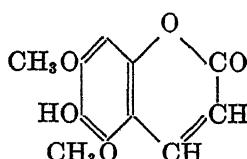
Fraxinol

Recently, Späth (234) has found that a series of trihydroxycoumarins are present in the form of their glucosides in the fresh bark of German ashwood. Of these, the coumarins fraxidin and isofraxidin are related to fraxetin. Fraxetin, fraxidin, and isofraxidin are the derivatives of 1,2,3,4-tetrahydroxybenzene, while fraxinol is a derivative of 1,2,3,5-tetrahydroxybenzene.

Coumarins with hydroxyl groups in the pyrone ring have not yet been found as natural products, but 4-hydroxy-7-methoxycoumarin is produced by the thermal decomposition of neutral constituents of ammonia gum (125).

Osthol, osthenol, ostruthin, ammoresinol, and toddalolactone belong to the group of hydroxy- and methoxy-coumarins with alkyl or alkylene groups. Osthol, found to occur in umbelliferous plants, is the methyl ether of osthenol, which is 7-hydroxy-8-(γ,γ-dimethylallyl)coumarin (243). Späth has investigated various plant materials to find other coumarins with constitutions analogous to that of osthol.

Another interesting coumarin belonging to this group is ostruthin, occurring in imperatoria rhizomes as a main coumarin (237).

The isolation and investigation of the constituents of umbelliferous resins which are reputed to be drugs is a difficult task, which is yet in its initial stage. Casparis (35) has devised a process by which a crystalline product called ammoresinol is obtained as a main constituent from ammonia rosin of *Dorema ammoniacum* Don., and it has been assigned the following constitution:

Osthenol

Ammoresinol
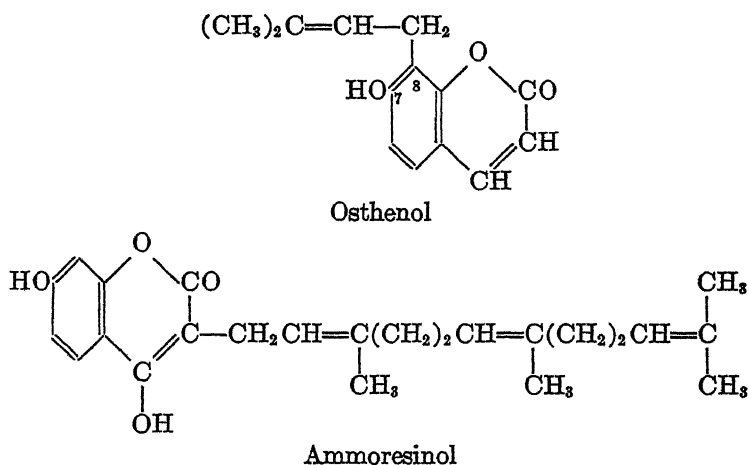
The optically active toddalolactone, isolated from the root-bark of *Toddalia aculeata* (Rutaceae) by Dey and Pillai (69), has been assigned the following constitution by Späth, Dey, and Tyray (229):
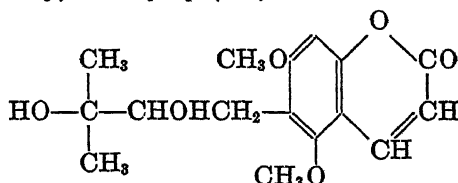
Furanocoumarins of type I have been found in nature.   Depending upon the position of fusion of the furan ring, several isomers are possible, two of which have been found to occur in nature,—angelicin (II) and psoralene (I).   These
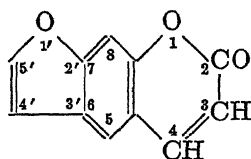
I
Psoralene
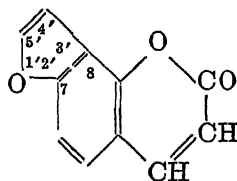
II
Angelicin

are the parent substances of several natural furanocoumarins.   The ring system of angelicin is present in isobergaptene and pimpinellin, while that of psoralene is found in bergaptol, bergaptene, xanthotoxol, xanthotoxin, isopimpinellin, imperatorin and isoimperatorin, oxypeucedanin, and ostruthol.

Angelicin was first detected in *Angelica archangelica* (Umbelliferae) and is also found to occur in an Indian leguminous plant, *Psoralea corylifolia* L.   Angelicin has been proved to be furano-2′,3′,7,8-coumarin (II) (244).

Psoralene, isomeric with angelicin, was found by Manjunath (111) in the same leguminous plant and its constitution established as furano-2′,3′,7,6-coumarin (I) (241).   Psoralene is also found in the leaves of the fig and appears to be widely distributed.

Bergaptene and xanthotoxin contain a methoxyl group with the psoralene ring structure.   Both of them are thus monomethoxy derivatives of psoralene. They occur in *Fagara* (Rutaceae) and other plants.   The determination of the correct structure for xanthotoxin from several suggested possible formulae is due to Thoms (254).
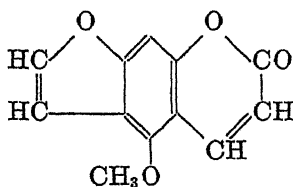
Bergaptene
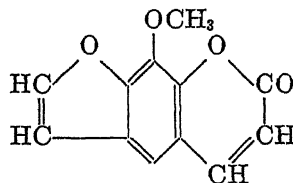
Xanthotoxin

Bergaptol, the hydroxy derivative of bergaptene, is found to occur along with bergaptene in bergamot oil; xanthotoxol, the hydroxy derivative of xanthotoxin, was isolated from the seeds of *Angelica archangelica*.   These phenolic furano-coumarins give on methylation bergaptene and xanthotoxin, respectively; thus their constitutions are beyond doubt.

Isobergaptene was found as a constituent in the roots of burnet saxifrage (*Pimpinella saxifraga*) and is 5-methoxyangelicin (264a).

Pimpinellin and isopimpinellin are dimethoxyfuranocoumarins obtained from the roots of burnet saxifrage.   The synthesis of isopimpinellin from 5,8-dihydroxypsoralene settles its constitution out of a plethora of suggested formulae (264).
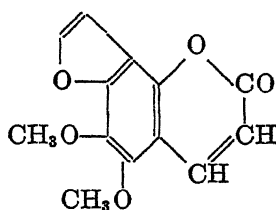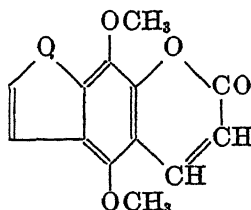
Pimpinellin   Isopimpinellin

Sphondin and sphondylin, found in the roots of bear's breech (*Acanthus mollis*), are methoxyfuranocoumarins whose constitutions have not been settled (246).

A number of complex furanocoumarins are present in master-wort (imperatoria) rhizome.   Of these, imperatorin, isoimperatorin, oxypeucedanin, and ostruthol have been completely investigated.   Imperatorin and isoimperatorin are isomeric (233, 239).   Oxypeucedanin, present in the roots of *Peucedanum officinale* (Umbelliferae) and known for nearly a century, has been investigated only in recent years (236).   Its name is misleading, as it would indicate that the substance is related to peucedanin, a furanocoumarin belonging to an entirely different group.   Ostruthol has been established as a furanocoumarin related to oxypeucedanin (227).
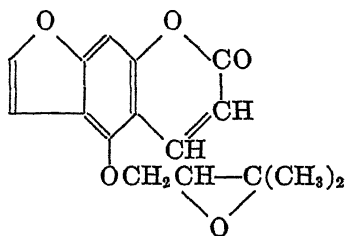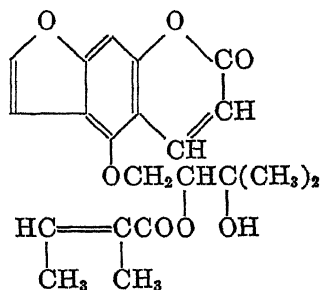
Oxypeucedanin   Ostruthol

All the above furanocoumarins are unsubstituted in the furan ring.   We shall now refer to a group of furanocoumarins with substituents in the furan ring, *viz.*, peucedanin, oreoselone, nodakenin, and nodakenetin.   In 1833, the presence of peucedanin in the rhizomes of *Peucedanum officinale* was noted, but Späth (238) took up the investigation of the structure of this product only a decade ago. This work gave him an incentive for his future work in the field of natural coumarins.

Peucedanin contains one methoxyl group more than oreoselone, while oreo-

selone has no free hydroxyl group; therefore Späth has put forward the following formulae for them:

CH_3
CH_3
CH—C
H O O
OC CO
CH
CH

Oreoselone

CH_3
CH_3
CH—C
O O
C CO
CH_3O
CH
CH
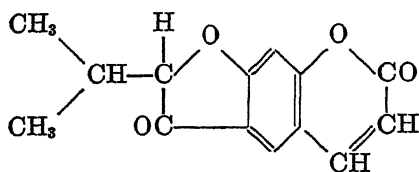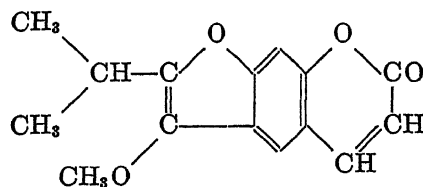
Peucedanin

Peucedanin is the enolic methyl ether of oreoselone, a fact which easily explains the hydrolysis of peucedanin to oreoselone.

Nodakenin is a coumarin glucoside found in a Japanese species of *Peucedanum decurvisum* Max., which on hydrolysis gives nodakenetin and *d*-glucose. Nodakenetin was also obtained in a minute quantity by Späth from the same plant (235).

$ROCH_2$
CH_3
CHC
HC
O O
CO
CH
CH
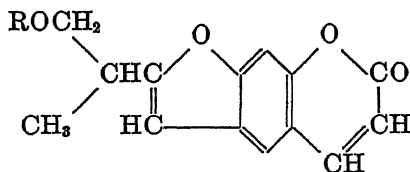
Nodakenetin (R = H)
Nodakenin (R = $C_6H_{11}O_5$)

Späth, Bose, and others (225) have isolated seselin from *Seseli indicum* and have assigned the following structure to it. The same coumarin is also obtained from Japanese *Skimmia japonica*.

HC
$(CH_3)_2C$
CH
O
O
CO
CH
CH
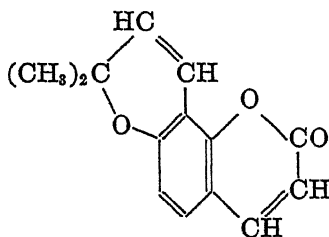
Seselin

Xanthoxyletin (or xanthoxylin N) and xanthyletin, occurring in the bark of the plant *Xanthoxylum americanum* (Rutaceae), belong to the group of coumarins with a 2,2-dimethyl-1,2-chromene ring. At present two coumarins are known in this group. Xanthoxyletin has now been found to occur in *Luvunga scandeus* Ham. Robertson (174) has done much work on these coumarins, and assigned the following structures to them:
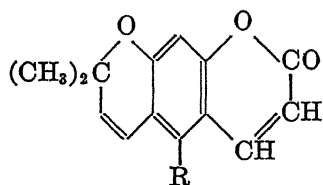
Xanthyletin (R = H)
Xanthoxyletin (R = OCH$_3$)

Synthesis

The natural coumarins, umbelliferone, herniarin, citropten, esculetin, and daphnetin, were long ago synthesized by the well-known methods of Perkin and Pechmann. The synthesis of these coumarins presented some difficulties, as the necessary starting materials were not easily available then. During the last few years, Seka (182) and Robertson (25) have synthesized scopoletin from 2,4-dihydroxy-5-methoxybenzaldehyde; Späth and Jerzmanowska (234) have obtained fraxinol from 3,6-dihydroxy-2,4-dimethoxybenzaldehyde.

For synthesizing the glucosides of phenolic coumarins, the reaction with aceto-bromoglucose has been found to be fruitful in several cases. Seka (181) and Merz (140) synthesized cichoriin from esculetin; Merz (140; also 138) prepared a pure specimen of scopolin. Mauthner (139) has prepared a synthetic umbelliferone glucoside isomeric with skimmin. Leone (127) obtained a daphnetin glucoside isomeric with natural daphnin. From helicin, a glucoside of salicylaldehyde, Shinoda and Imaida (210) have synthesized melilotoside by condensation with malonic acid.

In the group of alkylated hydroxycoumarins, Späth and coworkers (247) have carried out the synthesis of osthol by subjecting the product of the action of γ,γ-dimethylallyl bromide on the sodium salt of 2-hydroxy-4-methoxybenzaldehyde to the Perkin reaction. By the action of malic and sulfuric acids on the monomethyl ether of 2-isoamylresorcinol, dihydroösthol is obtained, from which osthol has been prepared. Hailer and Acree (94) also carried out a similar synthesis.
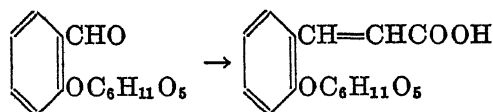
Melilotoside
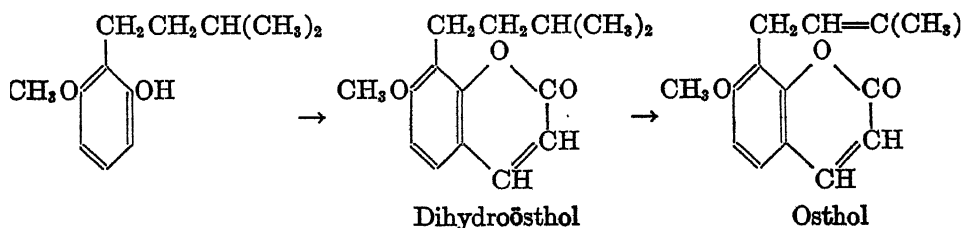
Dihydroösthol   Osthol

With regard to the synthesis of natural furanocoumarins, Späth prepared angelicin in low yield by treating the sodium salt of umbelliferone with bromoacetal at a high temperature.   Späth and Pailer improved the yield by building the furan ring on umbelliferone-8-aldehyde.   Limaye (131) synthesized angelicin from 4-hydroxycoumarone.

Psoralene has been synthesized by Späth, Manjunath, Pailer, and Jois (241) from 6-hydroxycoumarone.   The coumarone does not undergo the Pechmann reaction, but the 6-hydroxycoumaran, when treated with malic and sulfuric acids, formed the coumarin ring; the dihydropsoralene thus obtained was dehydrogenated to psoralene.

Dihydropsoralene   Psoralene
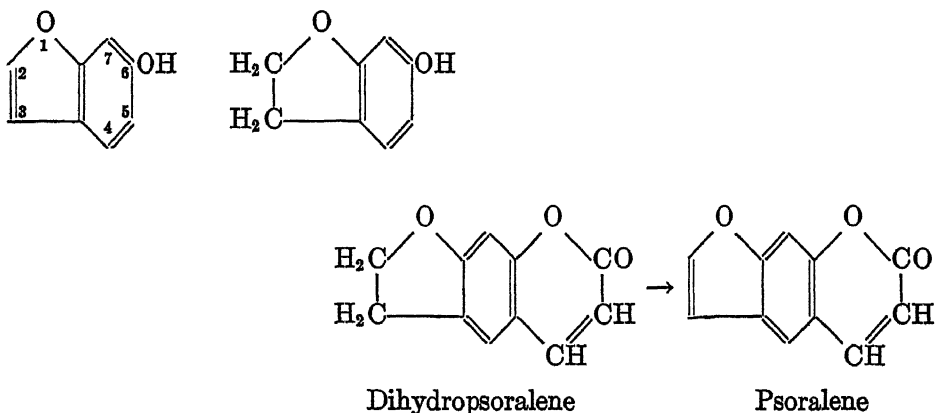
Späth and Pailer synthesized xanthotoxol from 6,7-dihydroxycoumaran, which on condensation with malic acid in the presence of sulfuric acid gave dihydroxanthotoxol; dehydrogenation of this substance yielded xanthotoxol.   To get xanthotoxin, either xanthotoxol was methylated or dihydroxanthotoxol was first methylated and then dehydrogenated.

Xanthotoxin
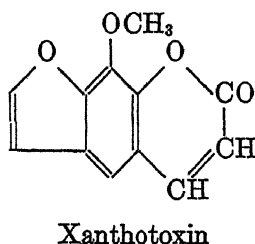
Späth, Wessely, and Kubiczek (248) have synthesized bergaptol, starting with 3,4,6-triacetoxycoumarone.   This substance was hydrogenated, and the coumaran treated with ethyl sodioformylacetate in alkaline solution.   Deacetylation took place, and the resulting hydroxy compound condensed with the forma-

tion of two products, allobergaptol and bergaptol, which on methylation gave allobergaptene and bergaptene, respectively. Isobergaptene is produced by the opening of the pyrone ring of bergaptol, partial methylation of the resulting product, and new ring formation in another position (240).

Howell and Robertson (109) have synthesized bergaptene starting with apoxanthoxyletin: 7-hydroxy-5-methoxy-6-formylcoumarin condensed with bromoacetic ester to yield a product which on hydrolysis gave the acid which, on cyclization and simultaneous decarboxation, yielded bergaptene. Foster, Howell, and Robertson (82) have synthesized allobergaptene.

Bergaptol (R = H)
Bergaptene (R = CH₃)

Allobergaptol (R = H)   Isobergaptene
Allobergaptene (R = CH₃)
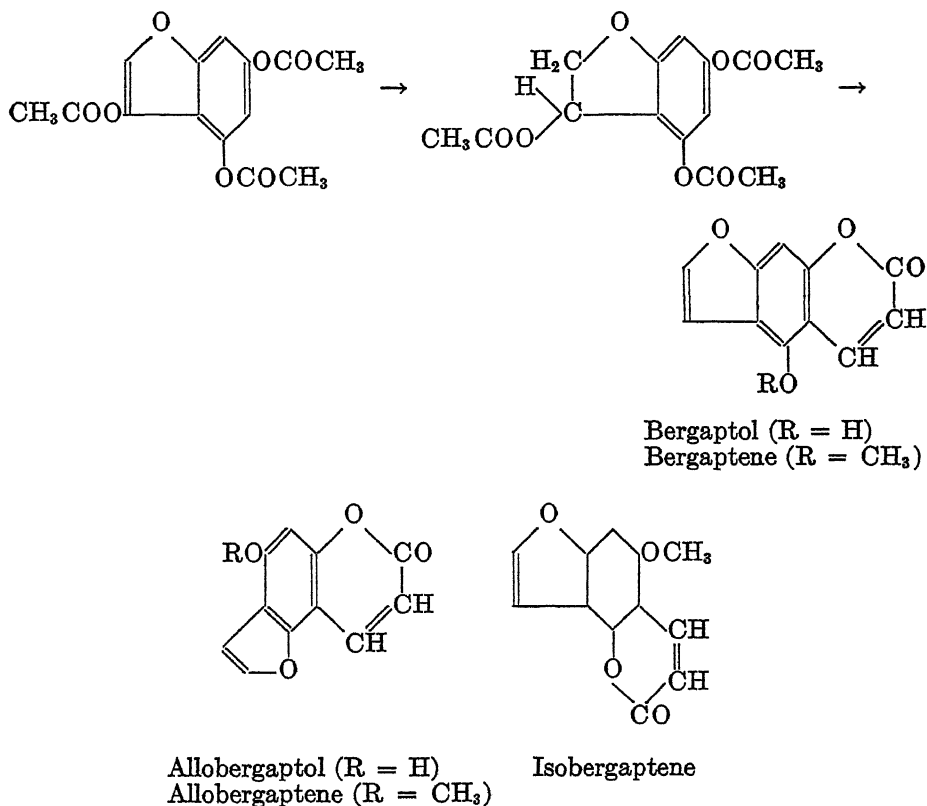
By the action of perbenzoic acid on isoimperatorin, Späth and Holzen (232) obtained oxypeucedanin. By the condensation of prenyl bromide with bergaptol in the presence of sodium methylate, Späth and Dobrovolny (228) prepared isoimperatorin, thus establishing a total synthesis of oxypeucedanin.

Wessely and Nadler (264a) have carried out a synthesis of isopimpinellin. Starting with bergaptene and xanthotoxin, they prepared their nitro derivatives;

Bergaptol → Isoimperatorin

methylation ↓

Bergaptene

Oxypeucedanin

Isopimpinellin ← Xanthotoxin
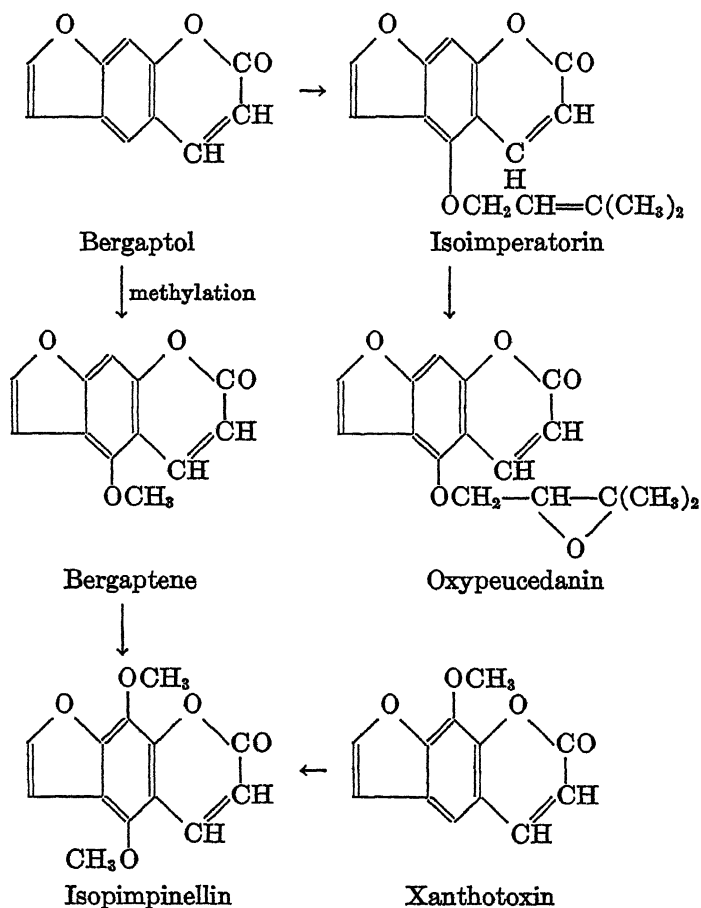
from these derivatives quinones were prepared, which on reduction and subsequent methylation gave isopimpinellin.

Späth and Hillel (231) have obtained seselin by heating umbelliferone with 2-methyl-3-butyn-2-ol.

Späth and Schmid (245) have recently synthesized luvangetin from 1,3,2-$C_6H_3(OH)_2OCH_3$.

Luvangetin
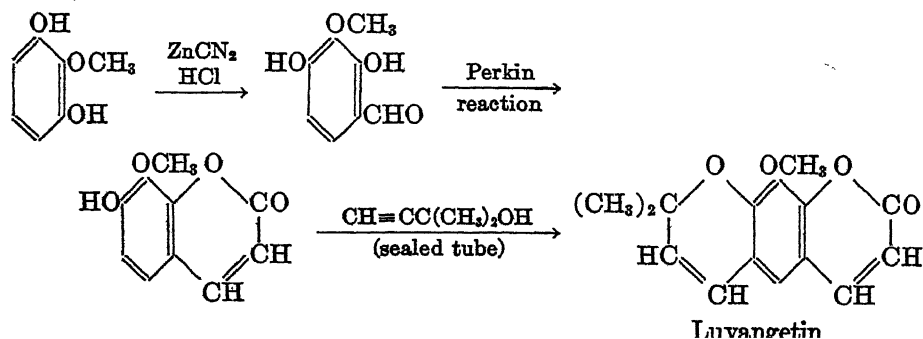
X. Physiological Action of Coumarins

Coumarins have been found to be physiologically effective for animals as well as men. Levaditti, Ellinger, Bergstrom, Rai, and Trendenburg have done the main work in this field. A collective bibliography of the relevant literature is available in E. Merck's *Jahresbericht* (262).

It has been observed that coumarin acts as a narcotic for rabbits, frogs, earthworms, and many other animals. It is a sedative and hypnotic for mice. In men as well as dogs its toxic action is predominant. A dose of about 5 g. kills a sheep; the fatal dose for horses and cattle is about 40 g.

Wasicky has investigated the action of naturally occurring coumarins such as pimpinellin, peucedanin, and ostruthin on the mouse, rat, and guinea pig. They have been found to possess a little toxicity. It was also observed that they promote the intestinal absorption of other substances. Priess, Rost, and Sieburg have studied the action of natural coumarins on fish. Incidental to their purely chemical work on natural coumarins, Späth and Kuffner have carried out a number of experiments on fresh-water fish (*Lebistes reticulatus*). They found that these coumarins are highly effective substances in spite of the low concentration of solutions employed (owing to the fact that most of them are sparingly soluble). Initially they are strong stimulants but then the action becomes moderate. Fish gradually lose their balance, and remain steady or swim on their backs; movement is then suspended, and finally they die. The concentration of the dose by which the lethal effect set in after some hours was decidedly dependent on the constitution of the coumarin used. Whereas coumarin itself was first lethal in a concentration of 1 g. in 6800 cc. of water, the same effect was observed for the methyl ether of alloimperatorin in a concentration of 1 in 100,000. The absolute quantity of the coumarins which produced the effect on the fish used in these experiments was extraordinarily small. Altogether forty coumarins have been tested. Many of them show a poisonous effect like that of picrotoxin. The hydroxycoumarins have been found to be less effective, though toxicity increases considerably on methylation.

Coumarin, 3-chlorocoumarin, and particularly angelicin show a strong narcotic action on fish. In about 30 to 100 sec. after the administration of the dose, the fishes turned on their backs, remained without any recognizable injury for about 12 hr., gave response to stimulus when knocked, but again returned to their normal positions in fresh water.

For human beings, coumarin has a slight toxic effect. The first dose, to the extent of 4 g., produces the symptoms of illness and weakness. It has no definite injurious effect on the heart; it checks the reactivity of the sympathetic nerves and paralyzes the flat muscles. Dihydrocoumarin, o-hydroxyphenylpropyl alcohol, and chroman have a narcotic action. Werder has synthesized over one hundred derivatives of coumarin-3-carboxylic acids. (These acids have not yet been found to occur in the vegetable kingdom.) He has investigated their utility as medicines. They are sedative in small doses and hypnotic in large doses. Among the derivatives of these acids, the diethylamide has proved to be a good drug in general nervous diseases and in various neurasthenic and hysterical ailments.

Mannich has found that some hydroxycoumarins possessing the power of absorbing ultraviolet light are extensively used as medicinals in skin diseases. Recently β-methylesculetin has been used as an expectorant.

Asai (10) has published an interesting investigation on the action of daphnin for plants. He has shown that the leaves of the plant *Daphne odora* Thu. contain varying quantities of daphnin according to the period of vegetation. The falling leaf-buds contain 21–7 per cent of daphnin (on the basis of the dried material), while the developed buds contain only 6–7 per cent; the value finally declines to 1–3 per cent and remains constant until the leaves fall. Asai concludes that daphnin in the plant plays the important rôle of protecting the plant from the harmful effects of the short-wave radiations.

XI. Isocoumarins and Thiocoumarins

Isocoumarins, the lactones of benzenecarboxylic acids with a hydroxylated side chain unsaturated in the β-position, are isomeric with coumarins, the lactones of *o*-hydroxycinnamic acids.
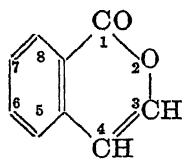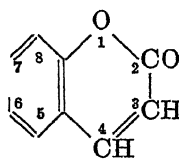
Isocoumarin   Coumarin

There is hardly any general method for the synthesis of isocoumarins, yet a good amount of work has been carried out and a number of isocoumarin derivatives have been synthesized. Bamberger and his coworkers (21, 22) obtained isocoumarin from β-naphthoquinone by oxidation with bleaching powder; *o*-carboxyphenylglyceric acid (I) was formed, which on heating with hydrochloric acid gave isocoumarin-3-carboxylic acid (II), the silver salt of which when heated yielded isocoumarin. Working along similar lines, Zincke (271) also obtained isocoumarin. Gabriel (90) synthesized isocoumarin in small quantity from nitromethylenephthalide (III) by boiling it with hydriodic acid.
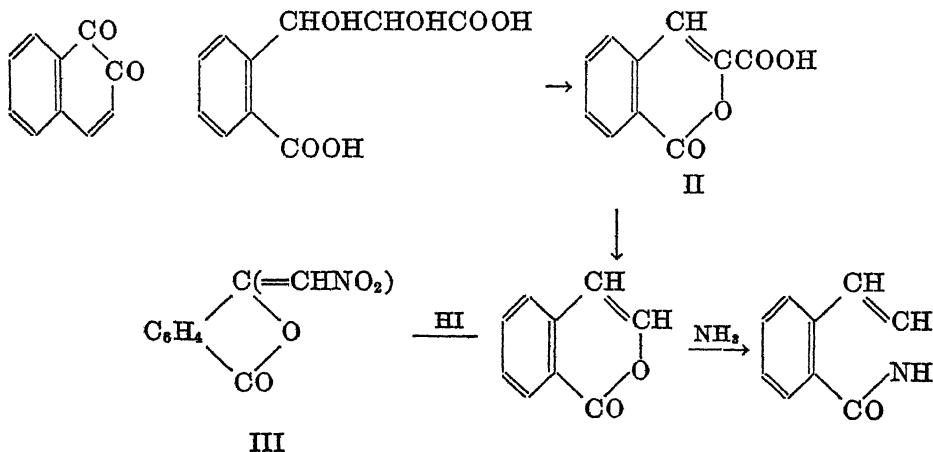
Isocoumarins are useful materials for synthesizing isocarbostyrils, since on treatment with ammonia, the oxygen of the heterocyclic ring is easily replaced by the $=$NH group.

Jowett and Pyman (112), during the course of their investigations on the physiological action and chemical constitution of tropeines, synthesized iso-coumarincarboxyltropeine in a manner analogous to that of Bamberger.

$$\text{(R = —COC}_8\text{H}_{14}\text{ON)}$$
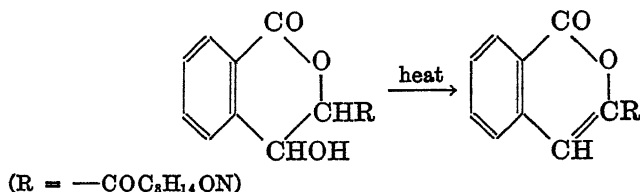
Dieckmann and Meiser (80) obtained ethyl isocoumarin-4-carboxylate and its free acid by heating ethyl hydroxymethylenehomophthalate:

$$\text{(R = C}_2\text{H}_5 \text{ or H)}$$
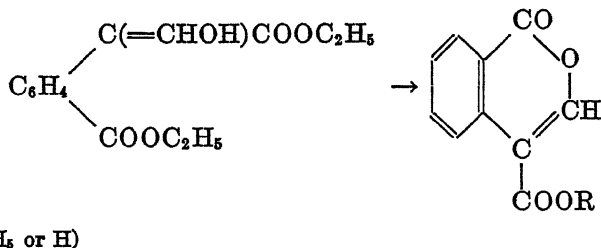
Fritsch (89) synthesized trihydroxymethylisocoumarin from gallacetol, the condensation product of gallic acid and chloroacetone, by treating it with concentrated sulfuric acid.
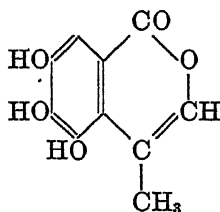
Bain, Perkin (Jr.), and Robinson (13) tried to develop a general method of isocoumarin synthesis depending upon the hydrolysis of the condensation product of hippuric acid with o-aldehydo acids, using acetic anhydride as condensing agent, but the hydrolysis did not occur in the manner expected. However, they were able to obtain 3-benzoyl-7,8-dimethoxyisocoumarin by the alkaline hydrolysis of ω-opianoylacetophenone:
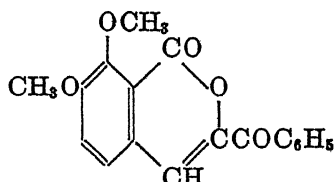
Davies and Poole (53), during their studies on homophthalyl chloride, obtained 3-chloroisocoumarin and 3,3,4,4-tetrachloro-3,4-dihydroisocoumarin by the action of phosphorus pentachloride on homophthalic acid, the explanation of its production being the existence of homophthalic anhydride in the enolic form.
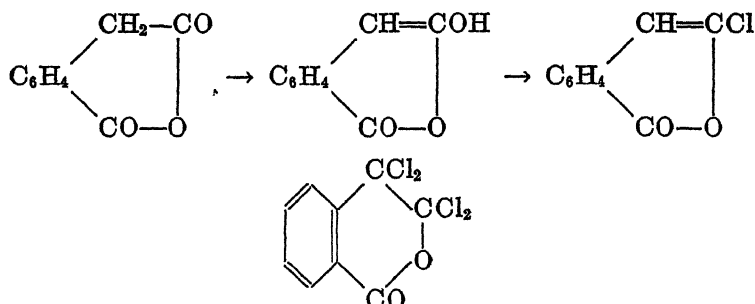
By the action of alkali on acetylated or benzoylated 3-methylindan-1,2-dione oxime, Heller (98) obtained an acid which on treatment with acetic anhydride and sodium acetate gave 3,4-dimethylisocoumarin.
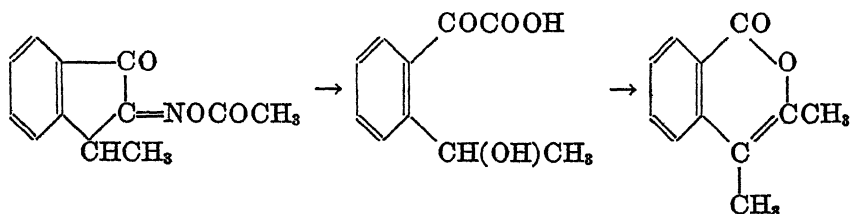
A characteristic isocoumarin derivative called berganin was isolated by Tschitschibabin (259) from the root stems of various members of the saxifrage family. The following formula has been proposed for it:
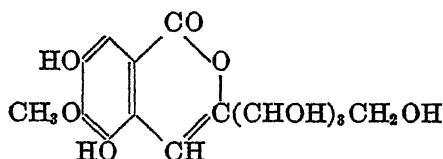
If either of the two oxygen atoms of the heterocyclic ring of the coumarin derivative is replaced by a sulfur atom, a thiocoumarin is formed. Tiemann (255) heated a mixture of coumarin and phosphorus pentasulfide at 120°C. and isolated thiocoumarin (A):

A
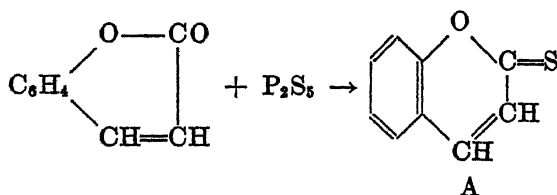
Aldringen (11) extended this reaction to several coumarins and obtained similar thiocoumarins. Clayton (49) prepared various thiocoumarins in a similar manner. Chmelewski and Friedlander (46) synthesized *o*-thiolcinnamic acid and dehydrated it to thiocoumarin (B).

$$C_6H_4 \begin{matrix} SH \\ \\ CH=CHCOOH \end{matrix} \xrightarrow{-H_2O} \quad B$$
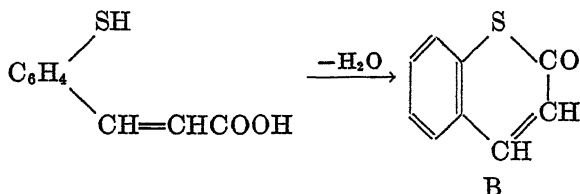
REFERENCES

(1) ADAMS, R., McPHEE, W. D., CARLIN, R. B., AND WICKS, Z. W.: J. Am. Chem. Soc. **65**, 356 (1943).

(1a) ADAMS, R., AND MECORNEY, J. W.: J. Am. Chem. Soc. **66**, 802 (1944).

(2) AHMED, S., AND DESAI, R. D.: Proc. Indian Acad. Sci. **5A**, 277 (1937).

(3) AHMED, S., AND DESAI, R. D.: Proc. Indian Acad. Sci. **6A**, 7 (1937).

(4) ALGAR, J., BARRY, V. C., AND TWOMEY, T. F.: Proc. Roy. Irish Acad. **41**, 8 (1932).

(5) ALI, S. A., DESAI, R. D., AND SHROFF, H. P.: Proc. Indian Acad. Sci. **13A**, 184 (1941).

(6) ALLAN, J., AND ROBINSON, R.: J. Chem. Soc. **1924**, 2192.

(7) ANSCHÜTZ, R.: Ann. **367**, 169 (1909).

(8) ANSCHÜTZ, R.: Ann. **368**, 23 (1910).

(9) APPEL, H.: J. Chem. Soc. **1935**, 1031.

(10) ASAI, T.: Acta Phytochim. **5**, 9 (1930–31).

(11) ALDRINGEN, F.: Ber. **24**, 3459 (1891).

(12) BADHWAR, I. C., BAKER, W., MENON, B. K., AND VENKATRAMAN, K.: J. Chem. Soc. **1931**, 1541.

(13) BAIN, D., PERKIN, W. H., JR., AND ROBINSON, R.: J. Chem. Soc. **1914**, 2392.

(14) BAKER, W.: J. Chem. Soc. **1925**, 2349.

(15) BAKER, W.: J. Chem. Soc. **1933**, 1381.

(16) BAKER, W.: J. Chem. Soc. **1934**, 1684: Annual Reports of the Progress of Chemistry **33**, 283 (1936).

(17) BAKER, W., AND EASTWOOD, F. M.: J. Chem. Soc. **1929**, 2900.

(18) BAKER, W., AND LOTHIAN, MISS O. M.: J. Chem. Soc. **1935**, 628.

(19) BAKER, W., AND ROBINSON, R.: J. Chem. Soc. **1925**, 1981.

(20) BALAIAH, V., SESHADRI, T. R., AND VENKATESWARLU, V.: Proc. Indian Acad. Sci. **16A**, 68 (1942).

(21) BAMBERGER, E., AND FREW, W.: Ber. **27**, 207 (1894).

(22) BAMBERGER, E., AND KITSCHELT, M.: Ber. **25**, 892 (1892).

(23) BARGELLINI, G.: Atti. acad. Lincei [2] **178**, 261 (1925).

(24) BARGELLINI, G., AND MONTI, L.: Gazz. chim. ital. **45**, I, 90 (1915).

(25) BELL, J. C., AND ROBERTSON, A.: J. Chem. Soc. **1936**, 1828.

(25a) BENNEVILLE, P. L., AND CONNOR, R.: J. Am. Chem. Soc. **62**, 3067 (1940).

(26) BERGEL, F., JACOB, A., TODD, A. R., AND WORK, T. S.: J. Chem. Soc. **1938**, 1375.

(27) BERT, L.: Compt. rend. **214**, 230 (1942).

(28) BIGINELLI, P.: Gazetta **24**, 491 (1894).

(29) BORSCHE, W., AND STREITBERGER, F.: Ber. **37**, 3165 (1904).

(30) BRIDGE, W., CROCKER, A. J., CUBIN, T., AND ROBERTSON, A.: J. Chem. Soc. **1937**, 1530.

(31) BÜLOW, C.: Ber. **38**, 474 (1905).

(32) CANTER, F. W., CURD, F. H., AND ROBERTSON, A.: J. Chem. Soc. **1931**, 1255.

(33) CANTER, F. W., MARTIN, A. R., AND ROBERTSON, A.: J. Chem. Soc. **1931, 1877**.
(34) CANTER, F. W., AND ROBERTSON, A.: J. Chem. Soc. **1931**, 1875.
(35) CASPARIS, P., AND MICHEL: Schweiz. Apoth.-Ztg., Suppl. **62,** 33 (1924).
(36) CHADHA, T. C., MAHAL, H. S., AND VENKATRAMAN, K.: J. Chem. Soc. **1933,** 1459.
(37) CHAKRAVARTI, D.: J. Indian Chem. Soc. **8,** 129, 407 (1931).
(38) CHAKRAVARTI, D.: J. Indian Chem. Soc. **9,** 389 (1932).
(39) CHAKRAVARTI, D.: J. Indian Chem. Soc. **12,** 536 (1935).
(40) CHAKRAVARTI, D., AND BAGCHI, P. N.: J. Indian Chem. Soc. **13,** 689 (1936).
(41) CHAKRAVARTI, D., AND BANERJEE, B. C.: J. Indian Chem. Soc. **14,** 37 (1937).
(42) CHAKRAVARTI, D., AND BANERJEE, B. C.: J. Indian Chem. Soc. **13,** 619 (1936).
(43) CHAKRAVARTI, D., AND GHOSH, B.: J. Indian Chem. Soc. **12,** 622 (1935).
(44) CHAKRAVARTI, D., AND MAJUMDAR, B.: J. Indian Chem. Soc. **15,** 136 (1938); **16,** 389 (1939).
(45) CHAKRAVARTI, D., AND MAJUMDAR, B.: J. Indian Chem. Soc. **16,** 151 (1939).
(46) CHMELEWSKI, CH., AND FRIEDLANDER, P.: Ber. **46,** 1903 (1913).
(47) CHUDGAR, M. C., AND SHAH, N. M.: J. Univ. Bombay **11,** 113 (1942).
(48) CLAYTON, A.: J. Chem. Soc. **1908,** 2016.
(49) CLAYTON, A.: J. Chem. Soc. **1908,** 525.
(50) CLAYTON, A.: J. Chem. Soc. **1910,** 1397.
(51) COLLIE, J. N., AND CHRYSTALL, F. R.: J. Chem. Soc. **1907,** 1804.
(52) CZAPSKA-NARKEWIEZ, MME. W.: Bull. intern. acad. polonaise, Classe sci. math. nat. **1935A,** 445.
(53) DAVIES, W., AND POOLE, H. G.: J. Chem. Soc. **1928,** 1616.
(54) DECKER, H., AND FELLENBURG, T.: Ber. **40,** 3816 (1907).
(55) DECKER, H., AND FELLENBURG, T.: Ann. **346,** 300 (1907).
(56) DELIWALA, C. V., AND SHAH, N. M.: J. Chem. Soc. **1939,** 1250.
(57) DELIWALA, C. V., AND SHAH, N. M.: Proc. Indian Acad. Sci. **13A,** 352 (1941).
(58) DELIWALA, C. V., AND SHAH, N. M.: Proc. Indian Acad. Sci. **17A,** 7 (1943).
(59) DESAI, R. D.: Rasāyanam **1,** 155 (1938).
(60) DESAI, R. D., AND EKHLAS, M.: Proc. Indian Acad. Sci. **8A,** 567 (1938).
(61) DESAI, R. D., AND HAMID, S. A.: Proc. Indian Acad. Sci. **6A,** 185 (1937).
(62) DESAI, R. D., AND MAVANI, C. K.: Proc. Indian Acad. Sci. **15A,** 1, 11 (1942).
(63) DESAI, R. D., AND VAKIL, V. M.: Proc. Indian Acad. Sci. **12A,** 357 (1940).
(64) DEY, B. B.: J. Chem. Soc. **1915,** 1606.
(65) DEY, B. B., AND GOSWAMI, M. N.: J. Chem. Soc. **1919,** 531.
(66) DEY, B. B., AND KRISHNAMURTI, P.: J. Indian Chem. Soc. **4,** 197 (1927).
(67) DEY, B. B., AND KUTTI, V. A.: Proc. Natl. Inst. Sci. India **6,** 641 (1940).
(68) DEY, B. B., AND LAKSHMINARAYANAN, A. K.: J. Indian Chem. Soc. **9,** 153 (1932).
(69) DEY, B. B., AND PILLAY, P. P.: Arch. Pharm. **273,** 223 (1935).
(70) DEY, B. B., AND RADHABAI, K.: J. Indian Chem. Soc. **11,** 635 (1934).
(71) DEY, B. B., RAO, R. H. R., AND SANKARANARAYANAN, Y.: J. Indian Chem. Soc. **9,** 281 (1932).
(72) DEY, B. B., RAO, R. H. R., AND SESHADRI, T. R.: J. Indian Chem. Soc. **11,** 743 (1934).
(73) DEY, B. B., AND ROW, K. K.: J. Chem. Soc. **1924,** 554.
(74) DEY, B. B., AND ROW, K. K.: J. Indian Chem. Soc. **1,** 107, 277 (1924).
(75) DEY, B. B., SARKAR, I., AND SESHADRI, T. R.: J. Indian Chem. Soc. **3,** 187 (1927).
(76) DEY, B. B., AND SANKARANARAYANAN, Y.: J. Indian Chem. Soc. **8,** 819 (1931).
(77) DEY, B. B., AND SESHADRI, T. R.: J. Indian Chem. Soc. **8,** 247 (1931).
(78) DEY, B. B., AND SESHADRI, T. R.: J. Indian Chem. Soc. **4,** 189 (1927).
(79) DODGE, F. D.: J. Am. Chem. Soc. **38,** 446 (1916): **52,** 1724 (1930).
(80) DIEKMANN, W., AND MEISER, W.: Ber. **41,** 3253 (1908).
(81) DYSON, G.: J. Chem. Soc. **1887,** 63.
(82) FOSTER, R. T., HOWELL, W. N., AND ROBERTSON, A.: J. Chem. Soc. **1939,** 930.
(83) FRANCIS, F.: Ber. **39,** 3803 (1906).

(84) FRIES, K., AND KLOSTERMANN, W.: Ber. **39,** 871 (1906).
(85) FRIES, K., AND KLOSTERMANN, W.: Ann. **362,** 1 (1908).
(86) FRIES, K., AND LINDEMANN, H.: Ann. **404,** 67 (1914).
(87) FRIES, K., AND NOHREU, M.: Ber. **58,** 1027 (1925).
(88) FRIES, K., AND VOLK, W.: Ann. **379,** 90 (1911).
(89) FRITSCH, P.: Ber. **26,** 419 (1893).
(90) GABRIEL, S.: Ber. **36,** 573 (1903).
(91) GHOSAL, S. C.: J. Indian Chem. Soc. **3,** 105 (1926).
(92) GOSWAMI, S., AND DAS-GUPTA, H. N.: J. Indian Chem. Soc. **8,** 417 (1931): **9,** 91 (1932).
(93) GULATI, K. C., SETH, S. R., AND VENKATRAMAN, K.: J. Chem. Soc. **1934,** 1765.
(94) HALLER, H., AND ACREE, F.: J. Am. Chem. Soc. **56,** 1389 (1934).
(95) HANZSCH, A., AND ZURCHER, H.: Ber. **20,** 1328 (1887).
(96) HANTZSCH, A.: Ber. **19,** 2928 (1886).
(97) HEAD, F., AND ROBERTSON, A.: J. Chem. Soc. **1930,** 2434: **1931,** 1241.
(98) HELLER, G.: Ber. **68,** 1085 (1935).
(99) HEILBRON, I. M., BARNES, H., AND MORTON, R. A.: J. Chem. Soc. **1923,** 2559.
(100) HEILBRON, I. M., HEY, D. H., AND LOWE, A.: J. Chem. Soc. **1934,** 1311.
(101) HEILBRON, I. M., HEY, D. H., AND LYTHGOE, B.: J. Chem. Soc. **1934,** 1581; **1936,** 295.
(102) HEILBRON, I. M., HESLOP, R. N., AND HOWARD, G. F.: J. Chem. Soc. **1933,** 1263.
(103) HEILBRON, I. M., AND HILL, D. W.: J. Chem. Soc. **1927,** 1705.
(104) HEILBRON, I. M., AND HILL, D. W.: J. Chem. Soc. **1927,** 2005.
(105) HEILBRON, I. M., HILL, D. W., AND WALLS, H. M.: J. Chem. Soc. **1931,** 1701.
(106) HOESCH, K.: Ber. **48,** 1122 (1915).
(107) HORII, Z.: J. Pharm. Soc. Japan **59,** 201 (1939).
(108) HOUBEN, J.: Ber. **37,** 489 (1904).
(109) HOWELL, W. N., AND ROBERTSON, A.: J. Chem. Soc. **1937,** 293.
(110) JACOBSEN, S., AND GHOSH, B. N.: J. Chem. Soc. **1915,** 424, 959, 1051.
(111) JOIS, H. S., MANJUNATH, L., AND VENKATRAO, S.: J. Indian Chem. Soc. **10,** 41 (1933).
(112) JOWETT, H. A. D., AND PYMAN, F.: J. Chem. Soc. **1907,** 92.
(113) JORDAN, L. A., AND THORPE, J. F.: J. Chem. Soc. **1915,** 387.
(114) KANEVSKAJA, S., AND FEDOROWA, A. M.: Z. anal. Chem. **93,** 176 (1933).
(115) KARRER, P., AND COWORKERS: Helv. Chim. Acta **3,** 511 (1920).
(116) KARTHA, A. R. S., AND MENON, K. P.: Proc. Indian Acad. Sci. **18A,** 28 (1943).
(117) KHAN, A. A., KURIEN, P. N., AND PANDYA, K. C.: Proc. Indian Acad. Sci. **1A,** 440
     (1935) et seq.
(118) KIEWIET, T., AND STEPHENS, H.: J. Chem. Soc. **1931,** 639.
(119) KING, F. E., AND ROBERTSON, A.: J. Chem. Soc. **1934,** 403.
(120) KNOEVENAGEL, E.: Ber. **31,** 2585, 2596 (1898); **37,** 4461 (1904) et seq.
(121) KOSTANECKI, S., AND ROZYCKI, A.: Ber. **34,** 102 (1901).
(122) KOTWANI, N. G., SETHNA, S. M., AND ADWANI, G. D.: J. Univ. Bombay **10,** 143 (1942).
(123) KOTWANI, N. G., SETHNA, S. M., AND ADWANI, G. D.: Proc. Indian Acad. Sci. **15A,**
     441 (1942).
(124) KULKARNI, D. R., ALIMCHANDANI, R. L., AND SHAH, N. M.: J. Indian Chem. Soc. **18,**
     113, 123 (1941).
(125) KUNZ, K., AND HOOPS, L.: Ber. **69,** 2174 (1936).
(126) KURIEN, P. N., PANDYA, K. C., AND SURANGE, V. R.: J. Indian Chem. Soc. **11,** 823
     (1934).
(127) LEONE, P.: Gazz. chim. ital. **55,** 673 (1925).
(128) LIMAYE, D. B.: Ber. **67,** 12 (1934).
(129) LIMAYE, D. B. AND GANGUL, D. D.: Rasāyanam **1,** 65 (1936).
(130) LIMAYE, D. B.: Ber. **65,** 375 (1932).
(131) LIMAYE, D. B.: Rasāyanam **1,** 1–23 (1936): **1,** 187 (1939).
(132) LIMAYE, D. B., AND KELKAR, G. R.: Rasāyanam **1,** 26 (1936).
(133) LIMAYE, D. B., AND KULKARNI, K. M.: Rasāyanam **1,** 208 (1941).

(134) LIMAYE, D. B., AND PANSE, T. B.: Rasāyanam 1, 231 (1941).
(135) LIMAYE, D. B., AND SATHE, N. R.: Rasāyanam 1, 87 (1937): 1, 48 (1936).
(136) LÒWENBEIN, A., PONGRÁCZ, E., AND SPIESS, E. A.: Ber. 57, 1517 (1924).
(137) LÖWENBEIN, A., AND ROSENBAUM, B.: Ann. 448, 223 (1926).
(138) MACBETH, A.: J. Chem. Soc. 1931, 1288.
(139) MAUTHNER, F.: J. prakt. Chem. [2] 91, 174 (1915).
(140) MERZ, K.: Arch. Pharm. 270, 476 (1932); 271, 449 (1933).
(141) MILLER, W., AND KINKELIN, F.: Ber. 22, 1706 (1889).
(142) MILLS, W. H., AND NIXON, I. G.: J. Chem. Soc. 1930, 2510.
(143) MOOKERJEE, A., AND GUPTA, J.: Indian J. Phys. 13, 439 (1939).
(144) NAGAI, N.: Ber. 25, 1254 (1892).
(145) NAIK, K. G., DESAI, R. D., AND DESAI, H. R.: J. Indian Chem. Soc. 6, 83 (1929).
(146) NAIK, K. G., DESAI, R. D., AND TRIVEDI, R. K.: J. Indian Chem. Soc. 6, 801 (1929).
(147) NAIK, K. G., AND PATEL, A. D.: J. Chem. Soc. 1934, 1043.
(148) PANDYA, K. C., AND SODHI, T. S.: J. Univ. Bombay 8, 173 (1939).
(149) PAREKH, N. B., AND SHAH, R. C.: J. Indian Chem. Soc. 19, 335 (1942).
(150) PAREKH, N. B., AND SHAH, R. C.: J. Indian Chem. Soc. 19, 339 (1942).
(151) PAULI, H., AND LOCKEMANN, K.: Ber. 48, 28 (1915).
(152) PECHMANN, H.: Ber. 17, 929 (1884).
(153) PECHMANN, H., AND COHEN, J. B.: Ber. 17, 2137 (1884).
(154) PECHMANN, H., AND DUISBERG, C.: Ber. 16, 2119 (1883).
(155) PECHMANN, H., AND GRAEGER, E.: Ber. 34, 378 (1901).
(156) PECHMANN, H., AND HANCKE, E.: Ber. 34, 354 (1901).
(157) PECHMANN, H., AND KRAFT, E.: Ber. 34, 421 (1901).
(158) PECHMANN, H., AND OBERMILLER: Ber. 34, 666 (1901).
(159) PECHMANN, H., AND SCHAAL, M.: Ber. 32, 3690 (1899).
(160) PERKIN, W H.: J. Chem. Soc. 1868, 53; 1877, 388.
(161) PERKIN, W. H.: J. Chem. Soc. 1873, 37.
(162) PERKIN, W. H.: J. Chem. Soc. 1871, 37.
(163) PERKIN, W. H., JR., AND ROBINSON, R.: J. Chem. Soc. 1907, 1073.
(164) RAKOWER, E.: Acta Phys. Polon. 3, 415 (1934); Chem. Zentr. 1935, II, 32.
(165) RAMASWAMY, S.: Current Sci. 10, 197 (1941).
(166) RANGASWAMI, S., AND SESHADRI, T. R.: Proc. Indian Acad. Sci. 6A, 112 (1937);
        9A, 7 (1939).
(167) RANGASWAMI, S., AND SESHADRI, T. R.: Proc. Indian Acad. Sci. 12A, 375 (1940).
(168) RANGASWAMI, S., SESHADRI, T. R., AND VENKATESWARLU, V.: Proc. Indian Acad. Sci.
        13A, 316 (1941).
(169) RAU, M. A. G.: Current Sci. 5, 132 (1936): Proc. Indian Acad. Sci. 4A, 687 (1936).
(170) RAY, J. N., SILOOJA, S. S., AND VAID, V. R.: J. Chem. Soc. 1935, 813.
(171) ROBERTSON, A., AND GOODALL, I.: J. Chem. Soc. 1936, 426.
(172) ROBERTSON, A., AND SANDROCK, W. F.: J. Chem. Soc. 1932, 1180.
(173) ROBERTSON, A., SANDROCK, W. F., AND HENDRY, C. B.: J. Chem. Soc. 1931, 2426.
(174) ROBERTSON, A., AND SUBRAMANIAM, T.: J. Chem. Soc. 1937, 286.
(175) ROBERTSON, A., WATERS, R. B., AND JONES, E. T.: J. Chem. Soc. 1932, 1681.
(176) ROW, L. R., AND SESHADRI, T. R.: Proc. Indian Acad. Sci. 11A, 206 (1940).
(177) RUHEMANN, S., AND COWORKERS: J. Chem. Soc. 1900, 984, 1119; 1901, 470, 918.
(178) SAKAI, I. T., AND KATO, C.: J. Pharm. Soc. Japan 55, 691 (1935).
(179) SCHIFF, H.: Ber. 5, 665 (1872).
(180) SCHONBERG, A., AND MUSTAFA, A.: J. Chem. Soc. 1943, 79.
(181) SEKA, R., AND KALLIR, P.: Ber. 64, 622 (1931).
(182) SEKA, R., AND KALLIR, P.: Ber. 64, 909 (1931).
(183) SEN, R. N., AND CHAKRAVARTI, D.: J. Indian Chem. Soc. 5, 433 (1928).
(184) SEN, R. N., AND CHAKRAVARTI, D.: J. Indian Chem. Soc. 6, 847 (1929).
(185) SEN, R. N., AND CHAKRAVARTI, D.: J. Am. Chem. Soc. 50, 2428 (1928).

(186) Sen, R. N., and Chakravarti, D.: J. Indian Chem. Soc. **6**, 793 (1929).
(187) Sen, R. N., and Chakravarti, D.: J. Indian Chem. Soc. **7**, 247 (1930).
(188) Seshadri, T. R.: Proc. Indian Acad. Sci. **8A**, 519 (1938).
(189) Seshadri, T. R.: J. Chem. Soc. **1928**, 166.
(190) Seshadri, T. R., and Rao, P. S.: Proc. Indian Acad. Sci. **4**, 163, 630 (1936).
(191) Seshadri, T. R., and Rao, P. S.: Proc. Indian Acad. Sci. **4A**, 157 (1936).
(192) Sethna, S. M.: J. Univ. Bombay **9**, 104 (1940).
(193) Sethna, S. M., Shah, N. M., and Shah, R. C.: Current Sci. **6**, 93 (1937).
(194) Sethna, S. M., Shah, N. M., and Shah, R. C.: J. Chem. Soc. **1938**, 228.
(195) Sethna, S. M., and Shah, R. C.: J. Indian Chem. Soc. **15**, 383 (1938): **17**, 37 (1940).
(196) Sethna, S. M., and Shah, R. C.: J. Chem. Soc. **1938**, 1066.
(197) Sethna, S. M., and Shah, R. C.: J. Indian Chem. Soc. **17**, 239, 487 (1940).
(198) Sethna, S. M., and Shah, R. C.: J. Indian Chem. Soc. **17**, 211 (1940).
(199) Shah, H. A., and Shah, R. C.: J. Chem. Soc. **1938**, 1832.
(200) Shah, H. A., and Shah, R. C.: J. Chem. Soc. **1939**, 132, 949; **1940**, 245.
(201) Shah, H. A., and Shah, R. C.: J. Indian Chem. Soc. **17**, 41 (1940).
(202) Shah, N. M.: J. Univ. Bombay **11**, 109 (1942).
(203) Shah, N. M., and Shah, R. C.: Ber. **71**, 2075 (1938).
(204) Shah, N. M., and Shah, R. C.: J. Chem. Soc. **1938**, 1424.
(205) Shah, N. M., and Shah, R. C.: Bombay **7**, 213 (1938).
(206) Shah, R. C.: Current Sci. **3**, 157 (1934).
(207) Shah, R. C., and Laiwalla, M. C.: J. Chem. Soc. **1938**, 1828.
(208) Shah, R. C., Sethna, S. M., Bannerjee, B. C., and Chakravarti, D.: J. Indian Chem. Soc. **14**, 717 (1937).
(209) Shah, R. H., and Shah, N. M.: J. Indian Chem. Soc. **19**, 481, 486, 489 (1942).
(210) Shimoda, J., and Imaida, M.: J. Chem. Soc. Japan **54**, 107 (1934).
(210a) Shriner, R. L., and Sharp, A. G.: J. Org. Chem. **4**, 575 (1939).
(211) Simonis, H.: Ber. **50**, 779 (1917).
(212) Simonis, H., and coworkers: Ber. **46**, 2014 (1913): **47**, 692, 2229 (1914).
(213) Simonis, H., and Peters, F.: Ber. **41**, 830 (1908).
(214) Simonis, H., and Remmert, P.: Ber. **47**, 2229 (1914).
(215) Simonis, H., and Wenzel, G.: Ber. **33**, 421, 1962 (1900).
(216) Smith, L. I., and Austin, F. L.: J. Am. Chem. Soc. **64**, 528 (1942).
(217) Smith, L. I., and Byers, D. J.: J. Am. Chem. Soc. **63**, 612 (1941).
(218) Smith, L. I., and Denyes, R. O.: J. Am. Chem. Soc. **58**, 304 (1936).
(219) Smith, L. I., and Dobrovolny, F. J.: J. Am. Chem. Soc. **48**, 1693 (1926).
(220) Smith, L. I., and Nichols, J.: J. Am. Chem. Soc. **65**, 1739 (1943).
(221) Smith, L. I., and Ruoff, P. M.: J. Am. Chem. Soc. **62**, 145 (1940).
(222) Sonn, A.: Ber. **50**, 1292 (1917).
(223) Sonn, A., and Patschke, E.: Ber. **58**, 97 (1925).
(224) Späth, E.: Ber. **70A**, 83 (1937).
(225) Späth, R., Bose, P. K., Matzke, J., and Guha, N. C.: Ber. **72**, 821 (1939).
(226) Spath, E., Bose, P. K., and Schlager, J.: Ber. **70**, 702 (1937).
(227) Späth, E., and Christiani, A. F.: Ber. **66**, 1150 (1933).
(228) Späth, E., and Dobrovolny, E.: Ber. **72**, 52 (1939).
(229) Späth, E., Dey, B. B., and Tyray, E.: Ber. **72**, 53 (1939).
(230) Späth, E., and Galinovsky, F.: Ber. **70**, 235 (1937).
(231) Späth, E., and Hillel, R.: Ber. **72**, 963 (1939).
(232) Späth, E., and Holzen, H.: Ber. **68**, 1123 (1935).
(233) Späth, E., and Holze, H.: Ber. **66**, 1137 (1933).
(234) Späth, E., and Jerzmanowska-Sienkiewiezowa, Z.: Ber. **70**, 698, 1019 (1937).
(235) Späth, E., and Kainrath, P.: Ber. **69**, 2062 (1936).
(236) Späth, E., and Klager, K.: Ber. **66**, 914 (1933).
(237) Späth, E., and Klager, K.: Ber. **67**, 859 (1934).

(238) SPÄTH, E., KLAGER, K., AND SCHLÖSSER, C.: Ber. **64,** 2203 (1931).
(239) SPÄTH, E., AND KAHOVEC, L.: Ber. **66,** 1146 (1933).
(240) SPÄTH, E., AND KUBICZEK, G.: Ber. **70,** 1253 (1937).
(241) SPÄTH, E., MANJUNATH, L., PAILER, M., AND JOIS, H. S.: Ber. **69,** 1087 (1936).
(242) SPÄTH, E., AND PAILER, M.: Ber. **68,** 941 (1935).
(243) SPÄTH, E., AND PESTA, O.: Ber. **66,** 754 (1933).
(244) SPÄTH, E., AND PESTA, O.: Ber. **67,** 853 (1934).
(245) SPÄTH, E., AND SCHMID, H.: Ber. **74,** 193 (1941).
(246) SPÄTH, E., AND SIMON, A. F. J.: Monatsh. **67,** 344 (1936).
(247) SPÄTH, E., TEKAI, S., AND MIYAJIMA, SH.: Ber. **67,** 262 (1934).
(248) SPÄTH, E., WESSELY, F., AND KUBICZEK, G.: Ber. **70,** 243, 478 (1937).
(249) STAHMANN, M. A., WOLFF, I., AND LINK, K. P.: J. Am. Chem. Soc. **65,** 2285 (1943).
(250) SULLIVAN, W. R., HUEBNER, C. F., STAHMANN, M. A., AND LINK, K. P.: J. Am. Chem. Soc. **65,** 2288, 2292 (1943).
(251) TAEGE, C.: Ber. **20,** 2109 (1887).
(252) TAHARA, Y.: Ber. **25,** 1292 (1892).
(253) TASAKI, T.: Acta Phytochim. **3,** 21 (1927).
(254) THOMS, H.: Ber. **44,** 3325 (1911); **45,** 3705 (1912).
(255) TIEMANN, F.: Ber. **19,** 1661 (1886).
(256) TIEMANN, F., AND HERZFIELD, H.: Ber. **10,** 283 (1877).
(258) TRIVEDI, P. L., SETHNA, S. M., AND SHAH, R. C.: J. Univ. Bombay **11,** 144 (1942).
(259) TSCHITSCHIBABIN: In Karrer's *Organic Chemistry*, page 508. Nordemann Publishing Co., Inc., New York (1938).
(260) WEISS, R., AND KRATZ, A.: Monatsh. **51,** 386 (1929).
(261) WEISS, R., AND MERKSAMMER, E.: Monatsh. **50,** 115 (1928).
(262) WERDER, F. W.: Merck's Jahresbericht **50,** 88 (1936).
(263) WESSELY, F., AND DEMMER, E.: Ber. **61,** 1279 (1928).
(264) WESSELY, F., AND KALLAB, F.: Monatsh. **59,** 161 (1932).
(264a) WESSELY, E., AND NADLER, E.: Monatsh. **60,** 141 (1932).
(265) WIDMANN, O.: Ber. **51,** 533 (1918).
(266) WILLSTÄTTER, R., AND SCHMIDT, O. T.: Ber. **57,** 1945 (1924).
(267) WITTENBURG, M.: J. prakt. Chem. **21,** 26 (1880).
(268) WITTIG, G.: Ber. **57,** 88 (1924).
(269) WITTIG, G., BANGERT, F., AND RICHTER, H. E.: Ann. **446,** 178 (1926).
(270) YANAGISAWA, H., AND KONDO, H.: J. Pharm. Soc. Japan **472,** 498 (1921).
(271) ZINCKE, TH.: Ber. **25,** 1493 (1892).

CONVERSION OF OXYGEN DERIVATIVES OF HYDROCARBONS INTO BUTADIENE

GUSTAV EGLOFF AND GEORGE HULLA

Universal Oil Products Company, Chicago, Illinois

CONTENTS

I. INTRODUCTION

The present study covers the production of butadiene (i.e., 1,3-butadiene) from oxygen derivatives of hydrocarbons. These derivatives are converted readily into butadiene by processes that involve one or more stages or units of

CHART I

Oxygen derivatives of hydrocarbons directly convertible into butadiene

ALKANOLS

Ethanol
2-Propanol
1-Butanol
2-Butanol
2-Methyl-1-propanol "Pentanol"*
3-Methyl-1-butanol
2-Methyl-2-butanol
3-Chloro-1-butanol
3-Chloro-2-butanol

CYCLANYLALKANOL

Cyclopropylcar-
binol

CYCLANOLS

Cyclobutanol
1-Methyl-3-cyclo-
pentanol
"Dimethylcyclo-
pentanols"
Cyclohexanol

ALKANEDIOLS

1,3-Butanediol
1,4-Butanediol
2,3-Butanediol

HYDROXYBENZENES

Hydroxybenzene
1,2-Dihydroxy-
benzene
1,3-Dihydroxyben-
zene
1,4-Dihydroxyben-
zene

ALKANETETROL

1,2,3,4-Butanetetrol

ALKENOLS

1-Propen-3-ol
1-Buten-3-ol
1-Buten-4-ol
2-Buten-1-ol

ALKENEDIOL

1-Butene-3,4-diol

DIALKYL ETHERS

Diethyl ether
Ethyl α-chloroethyl ether
Ethyl β-chloroethyl ether
Ethyl α-hydroxyethyl ether
Ethyl β-hydroxyethyl ether
Ethyl α-ethoxyethyl ether
Ethyl α-acetoxyethyl ether
Methyl α-methoxyethyl
ether
γ,γ'-Dihydroxydibutyl
ether
γ-Chlorobutyl γ'-hydroxy-
butyl ether

ALKYL ALKENYL ETHERS

Ethyl vinyl ether
Methyl α-vinyl-β-iodo-
ethyl ether
Ethyl α-vinyl-β-iodoethyl
ether
n-Propyl α-vinyl-β-iodo-
ethyl ether
Isobutyl α-vinyl-β-iodo-
ethyl ether

DIALKENYL ETHERS

Divinyl ether
Di(2-buten-1-yl) ether

EPOXYBUTANES

1,4-Epoxybutane
2,3-Epoxybutane

DIOXANE

4-Methyl-m-dioxane

ALKANALS

Ethanal
Butanal
2-Methylpropanal
3-Hydroxybutanal
(β-hydroxybutyr-
aldehyde)

ALKENAL

2-Butenal (croton-
aldehyde)

ALKANOIC ACIDS

n-Butyric acid
Isobutyric acid
Isovaleric acid

ALKENOIC ACIDS

Acrylic acid
Oleic acid
Elaidic acid
Calcium Δ β,γ-dihydromuconate

ALKADIENOIC ACID

2,4-Pentadienoic acid

MONOESTERS

1,3-Butanediol 3-acetate
1,3-Butanediol 1-β-hydroxybu-
tyrate
2-Buten-1-yl acetate
2-Buten-1-yl trichloroacetate

DIESTERS

1,3-Butanediol diacetate
2,3-Butanediol diformate
2,3-Butanediol diacetate
2,3-Butanediol sulfite
1,2,3,4-Butanetetrol
diformate
2,3-Butene bis(ethylxantho-
genic acid)

TRIESTERS

Natural glycerides

* "Amylalkohol" in original specification.

64

operation. In Germany, for example, butadiene has been produced from ethyne by a series of four unit operations involving three oxygen derivatives: ethyne → ethanal → 3-hydroxybutanal (β-hydroxybutyraldehyde) → 1,3-butanediol → butadiene. In the United States and the U.S.S.R., on the other hand, the same product is obtained from ethanol by a single-stage catalysis which may, however, actually involve intermediary formations of ethanal, 3-hydroxybutanal, and 1,3-butanediol. Chart I lists the various oxygen derivatives of hydrocarbons that have been converted into butadiene by single-stage processes. Butadiene can be obtained from aliphatic members and cyclic members, which will be considered in order of increasing number of hydroxyl groups, double bonds, and ring atoms.

The literature generally conveys the impression that 1,3-butadiene is produced as the only member of the C_4H_6 group of isomers (1,2-butadiene, 1,3-butadiene, 1-butyne, 2-butyne, methylenecyclopropane, methylcyclopropene, and cyclobutene). One cannot assert, however, that the isomers of 1,3-butadiene are completely absent without recourse to the new analytical tools, such as spectrographic analysis, now being extensively used. In this study butadiene means the 1,3- or conjugated isomer. A previous study considers the production of butadiene from hydrocarbons (21).

The conversion of ethanol, one of the primary sources of butadiene in the synthetic rubber program, to butadiene was discovered in 1901 by Professor Nef of the University of Chicago (116). In 1902 Professor Ipatieff, working independently at St. Petersburg, converted ethanol into butadiene (75). The first plants (37) for the dehydrogenation and dehydration of ethanol were installed in Russia in 1931; by 1938 some 100,000 short tons of butadiene synthetic rubber were being produced annually. In 1938 ethanol was used in Poland as a source material for butadiene synthetic rubber. During 1944 about 360,000 short tons of butadiene will be produced from ethanol in the United States (18). When this amount of butadiene is polymerized with styrene, the yield of Buna S synthetic rubber will be about 480,000 tons.

II. HYDROXY DERIVATIVES OF HYDROCARBONS

A. ALIPHATIC MEMBERS

1. Alkanols

(a) Development of ethanol conversion

Butadiene has been prepared from ethanol, 2-propanol, 1-butanol, 2-butanol, 2-methyl-1-propanol, 3-chloro-1-butanol, 3-chloro-2-butanol, 3-methyl-1-butanol, 2-methyl-2-butanol, and "pentanol," but only ethanol and the two unsubstituted butanols are known to yield appreciable amounts of it (23). Nef obtained a yield of 0.13 weight per cent of butadiene by passing ethanol over a zinc and pumice catalyst at 290–360°C. (116). Ipatieff obtained a yield of 0.85 weight per cent from ethanol which was passed over powdered aluminum at 580–680°C. (76). The latter yield is based upon the amount of tetrabromide formed, but the actual yield of butadiene was between 2 and 3 per cent of the

alcohol charged (77). Lebedev claimed that a process utilizing a mixture of zinc oxide and alumina at 400°C. (86, 87) gave an 18 per cent yield of butadiene, and a similar process using a zinc oxide and aluminum hydrosilicate catalyst at 410°C. (88) gave a 15 per cent yield. He also reported a yield of 15 per cent of butadiene from ethanol which was passed at 410°C. through a quartz tube containing zinc dust and floridin (fuller's earth) (92). Subsequent workers generally claimed higher yields but did not disclose the composition of the catalysts used (38, 43, 83, 89, 94, 95, 99, 100, 108, 150, 167, 168, 170).

Table 1 shows the progress made by the butadiene synthetic rubber industry in the U.S.S.R. (37, 170).

Synthetic rubber production in the United States depends largely upon butadiene (derived from ethanol and petroleum fractions) and styrene, which were used for the production of 765,000 long tons of Buna S in the year 1944 (table 2).

TABLE 1

The U.S.S.R. synthetic rubber industry

YEAR	SYNTHETIC RUBBER PRODUCTION	BUTADIENE FROM ETHANOL		SYNTHETIC RUBBER IN PER CENT OF TOTAL NEW RUBBER USED
	long tons	*per cent by weight*	*per cent of theory*	.
1933	5,600			4.7
1934	12,000			18.5
1935	20,000	23.5	40	40.6
1936	24,000		.	· 54.1
1937	50,000			73.1
1938	90,000	32.5	56	
1939 (early)		36.3	62	
1939 (late)		41	70	

According to Gilliland (42):

"In the alcohol process, grain alcohol or ethyl alcohol from other sources is used to produce a butadiene fraction of relatively high purity. . . . This type of operation is carried out in three plants designed for the Government program by the Carbide and Carbon Chemical Corporation. These plants will produce 220,000 short tons of butadiene per year. The first, located at Institute, West Virginia, and having a rated annual capacity of 80,000 short tons, has been completed for several months and is operating very successfully. The two other plants, located at Kobuta, Pennsylvania, and Louisville, Kentucky, and having rated annual capacities of 80,000 and 60,000 short tons, respectively, are now producing butadiene. . . .

"A different type of process for producing butadiene from alcohol is being constructed by the Bigler Chemical Company, employing the so-called Publicker, or Szukiewicz, process. This alcohol process apparently is fairly similar to the method employed by the Russians for the production of essentially all their butadiene.

"These alcohol processes produce from two to two and a half pounds of butadiene per gallon of 95 percent alcohol."

The quoted yield of butadiene is equivalent to 32–40 per cent by weight based on absolute alcohol.

(b) Lebedev's process

The "ideal" course of butadiene production from ethanol *per se* is given by the following over-all equation:

$$2CH_3CH_2OH \rightarrow CH_2{=}CH{-}CH{=}CH_2 + H_2 + 2H_2O$$
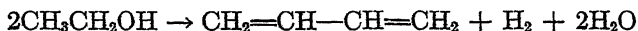
A catalyst mixture having a dehydrogenating component (A) and a dehydrating component (B) is specified. The present authors, however, are of the opinion that an individual catalyst with dehydrogenating and dehydrating properties would function in a similar manner. Lebedev (89) studied the effect of varying the catalyst composition from pure component A to pure component B and concluded that butadiene is formed from active forms of ethenol and of ethene. This theory appears unlikely when viewed in the light of data on ethanol and

TABLE 2

Production of synthetic rubber in the United States (18)

RUBBER	ACTUAL PRODUCTION 1943	ESTIMATED PRODUCTION 1944
	long tons	*long tons*
Buna S..	184,781	765,000
Butyl	1,373	26,200
Neoprene	33,603	53,200
Buna N.........	14,487	24,500
Total synthetic......	234,244	868,900

ethanal condensation. The requisite active forms (divalent radicals) were considered to develop through the dehydrogenation and dehydration of ethanol:

$$CH_3{-}CH_2OH \longrightarrow \overset{|}{CH_2}{-}\overset{|}{CHOH} + H_2$$

$$CH_3{-}CH_2OH \longrightarrow \overset{|}{CH_2}{-}\overset{|}{CH_2} + H_2O$$
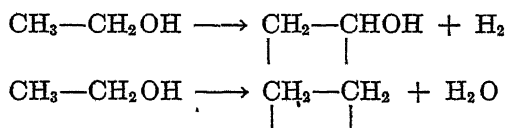
Reaction of active forms of ethenol with those of ethene, followed by dehydration of the two intermediates so formed, was considered to give butadiene:

$$CH_2{-}CHOH + CH_2{-}CH_2$$

$$CH_2{-}CHOH{-}CH_2{-}CH_2 \qquad CHOH{-}CH_2{-}CH_2{-}CH_2$$

$$CH_2{=}CH{-}CH{=}CH_2 + H_2O$$
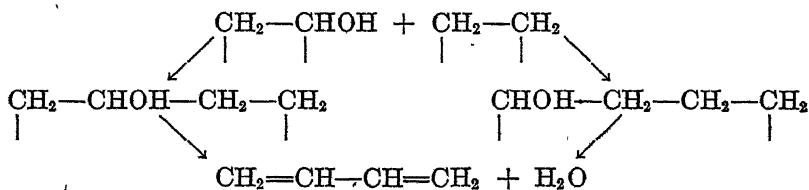
The foregoing formulation was based mainly on phenomena observed in the catalysis of ethanol over various mixtures of components A and B. Gradual addition of the dehydrating component B to dehydrogenating component A was attended by a rapid increase in the amount of butadiene to a maximum value,

corresponding to 25 per cent of B, followed by a rapid decrease to zero (see figure 1).

Lebedev pointed out that the amount of by-product ethanal was sharply diminished almost in proportion to the increase in butadiene content. Corresponding to the maximum on the butadiene curve, there was a sharply defined turn on the ethanal curve, indicating a connection between the processes of butadiene and ethanal formation, and a sharp break in the ethene curve. The content of butadiene diminished rapidly and that of ethene increased markedly as the catalyst composition approached that of the pure B component.
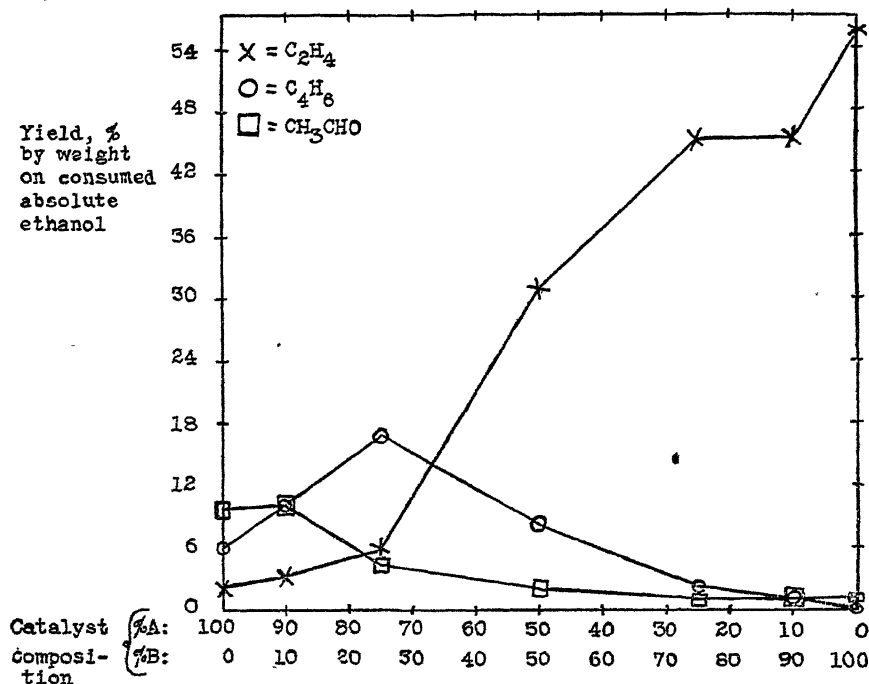
FIG. 1

Lebedev believed that

the reactions of formation of ethanal, ethene and butadiene are connected into a single system, and the assumption . . . highly plausible that butadiene is formed at the expense of the molecules of ethanal and ethene, but during a certain phase of the process preceding the completion of the reaction of formation of these molecules.

In support of the foregoing thesis, tabular and corresponding graphical data were presented covering the conversion of 90 per cent by volume ethanol at 435–445°C. over catalysts containing 0, 10, 25, 50, 75, 90, or 100 per cent of an undisclosed dehydrating component (table 3).

Balandin (1, 2) has applied his multiplet theory of catalysis to Lebedev's reaction and has concluded that the existence of ethenol radicals is impossible

on the basis of energy considerations. According to Balandin, ethanol is first dehydrogenated to ethanal; the latter condenses with ethanol to form butanediol, which loses two molecules of water to form butadiene.

Ostromyslenskiĭ discounted a union between ethene and ethanal (127):

This peculiar reaction [condensation of different alcohols with aldehydes accompanied by elimination of two molecules of water] was first observed in September, 1911. At that time, in private correspondence with O. G. Filippov concerning the new method by which he succeeded in preparing butadiene-1,3, the author indicated its preparation by dehydration of butanediol-1,3 and by condensation of ethene with ethanal. In the last-mentioned

TABLE 3

Conversion of ethanol into butadiene at 435–445°C. and approximately atmospheric pressure

		COMPOSITION OF THE CATALYST					
		100%A 0%B	90%A 10%B	75%A 25%B	50%A 50%B	25%A 75%B	10%A 90%B	0%A 100%B
Grams of ethanol (90% by volume) passed................		2800	2850	2800	2750	2900	2950	2800
Per cent of ethanol (90% by volume) recovered...		68.4	70.5	59.3	25.6	6.9	6.8	0.0
Per cent of ethanol (90% by volume) consumed..		31.6	29.5	40.7	74.4	93.1	93.2	100
Grams of condensate obtained ..		2650	2600	2450	1900	1500	1550	1400
Liters of gas obtained...		252	230	342	731	1021	1060	1193
Composition of the gas in per cent by volume	C_nH_{2n} ...	20.2	35.5	43.5	84.5	95.5	99.2	98.0
	H_2......	66.0	60.3	52.6	12.8	3.9	0.45	1.75
	CO.. ...	4.1	0.28	0.64	0.41	0.0	0.0	0.0
	CO_2	6.35	3.35	1.92	0.61	0.91	0.0	0.0
	CH_4... ..	1.58	0.0	0.42	0.40	0.0	0.0	0.0
Grams of butadiene contained in 1 liter of gas...		0.18	0.32	0.50	0.20	0.05	0.023	0.00
Yield of products in per cent by weight on consumed absolute ethanol	ethene......	2.25	3.08	5.85	31.0	45.3	45.5	55.7
	ether.	4.4	7.13	7.25	3.52	0.69	0.52	0.00
	ethanal.....	9.65	10.02	4.36	1.95	1.15	0.89	0.7
	hydrogen... .	1.72	1.57	1.59	0.45	0.14	0.018	0.07
	butadiene . .	5.8	10.1	16.6	8.2	2.26	0.99	0.00

case, the author assumed that when a mixture of ethanal and ethanol acts on alumina, the ethanol is first converted into ethene, which further reacts as follows:

$$CH_2{=}CH_2 + CH_3{-}CHO \rightarrow H_2O + CH_2{=}CH{-}CH{=}CH_2 \qquad (1)$$
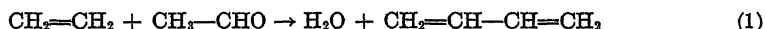
This assumption was quite plausible in view of V. N. Ipatieff's reaction. O. G. Filippov naturally understood the author's communication literally, and replied that he also observed formation of butadiene-1,3 under the action of a mixture of ethanal and ethene on alumina. Thus, O. G. Filippov observed the reaction (1) given above, which, incidentally, the present author so far did not succeed in repeating. Furthermore, in October, 1911, O. G. Filippov definitely stressed in his reply that in his opinion, formation of butadiene-1,3 from a mixture of ethanol and ethanal is impossible. Thus, the reaction

$$CH_3CHO + C_2H_5OH \rightarrow 2H_2O + CH_2{=}CH{-}CH{=}CH_2$$

was first observed by the author.

Ostromyslenskiĭ's earlier view, however, was that a mixture of ethene and ethanal may give higher yields of butadiene than does ethanol plus ethanal (133).

The present authors consider the probable function of the dehydration component in the catalyst mixture used in ethanol conversion to be the dehydration of two consecutive intermediary products, i.e., a butanediol and either a butenol or an epoxybutane (see sections on alkanediols, alkenols, and epoxybutanes):

$$2C_2H_5OH \rightarrow C_4H_8(OH)_2 + H_2$$

$$C_4H_8(OH)_2 \rightarrow C_4H_7OH(\text{or } C_4H_8O) + H_2O$$

$$C_4H_7OH(\text{or } C_4H_8O) \rightarrow C_4H_6 + H_2O$$

The intermediates to be considered in theories discounting the rôle of ethene include: 1,3- or 1,4- or 2,3-butanediol, 1-buten-3(or 4)-ol, 2-buten-1-ol, 1,3- or 1,4- or 2,3-epoxybutane, ethyl α-hydroxyethyl ether, ethyl α-ethoxyethyl ether, and ethyl vinyl ether. Theoretical formulation is restricted because of unknown rôles of tautomerization and catalytic isomerization among the several butenols *under the conditions* of Lebedev's process. Moreover, the actual or theoretical reaction velocities, activation energies, and heats of reaction for the initial, intermediary, and final steps of Lebedev's process are unknown or unreported.

Several theories can be formulated in place of Lebedev's explanation. The simplest explanation that the authors have devised is dehydrogenation (A) of ethanol, followed by conversion (B, C, or D) into 1,3-butanediol:

(A) $CH_3CH_2OH \rightarrow CH_3CHO + H_2$

(B) $CH_2OH—CH_2—H + CHO—CH_3 \rightarrow CH_2OHCH_2CHOHCH_3$

(C) $\begin{cases} CH_3CHO \rightleftarrows CH_2=CHOH \\ CH_2OH—CH_2—H + CH(OH)=CH_2 \rightarrow CH_2OHCH_2CHOHCH_3 \end{cases}$

(D) $\begin{cases} CH_3CHO \rightleftarrows CH_2=CHOH \\ CH(OH)=CH_2 + H—CHOH—CH_3 \rightarrow CH_2OHCH_2CHOHCH_3 \end{cases}$

1,3-Butanediol would form 1-buten-3(or 4)-ol, 2-buten-1-ol, or 1,3-epoxybutane, and these, considering the three sources of butanediol and its four mono-dehydration products, make possible twelve reaction paths, each of which could produce butadiene:

$$CH_2OHCH_2CHOHCH_3 \xrightarrow{(-H_2O)} \begin{cases} CH_2=CH—CHOH—CH_3 \\ CH_2=CH—CH_2—CH_2OH \\ CH_2OH—CH=CH—CH_3 \\ H_2C—CH—CH_3 \\ \quad | \quad \quad | \\ H_2C—O \end{cases}$$

$$\xrightarrow{(-H_2O)} CH_2=CH—CH=CH_2$$

The three reaction paths involving 2-buten-1-ol are related to Ostromyslenskiĭ's explanation of the ethanol and ethanal condensation (page 73), but his intermediary steps are purposely omitted.

Another explanation suggested by the present authors covers conversion through 1,4-butanediol:

$$CH_3CH_2OH \rightarrow CH_3CHO + H_2$$

$$CH_3CHO \rightleftarrows CH_2{=}CHOH$$

$$CH(OH){=}CH_2 + H{-}CH_2{-}CH_2OH \quad CH_2OHCH_2CH_2CH_2OH$$

$$CH_2OHCH_2CH_2CH_2OH \xrightarrow{(-H_2O)} \begin{bmatrix} CH_2{=}CH{-}CH_2 \quad CH_2OH \\ H_2C{-\!-\!-\!-}CH_2 \\ | \qquad\qquad | \\ H_2C \qquad\quad CH_2 \\ \diagdown \quad \diagup \\ O \end{bmatrix}$$

$$\xrightarrow{(-H_2O)} CH_2{=}CH{-}CH{=}CH_2$$

The 1,4-butanediol would form 1-buten-4-ol and 1,4-epoxybutane. Both of these monodehydration intermediates yield butadiene.

The authors postulate also four sequences of reactions (A + B + E + F; A + B + G + H + I; A + C + D + E + F; and A + C + D + G + H + I) proceeding via 2,3-butanediol:

(A) $CH_3CH_2OH \rightarrow CH_3CHO + H_2$

(B) $CH_3CHO + H{-}CHOH{-}CH_3 \rightarrow CH_3CHOHCHOHCH_3$

$\begin{cases} \text{(C)} \quad CH_3CHO \rightleftarrows CH_2{=}CHOH \\ \text{(D)} \quad CH_2{=}CHOH + H{-}CHOHCH_3 \rightarrow CH_3CHOHCHOHCH_3 \end{cases}$

(E) $CH_3CHOHCHOHCH_3 \rightarrow CH_2{=}CHCHOHCH_3 + H_2O$

(F) $CH_2{=}CHCHOHCH_3 \rightarrow CH_2{=}CH{-}CH{=}CH_2 + H_2O$

(G) $CH_3CHOHCHOHCH_3 \rightarrow CH_3CH{-}CHCH_3 + H_2O$.
$\qquad\qquad\qquad\qquad\qquad\qquad\qquad \diagdown\!\diagup$
$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\; O$

(H) $CH_3CH{-}CHCH_3 \rightarrow CH_2{=}CHCHOHCH_3$
$\quad\;\; \diagdown\!\diagup$
$\qquad O$

(I) $CH_2{=}CHCHOHCH_3 \rightarrow CH_2{=}CH{-}CH{=}CH_2 + H_2O$
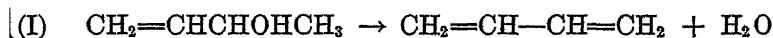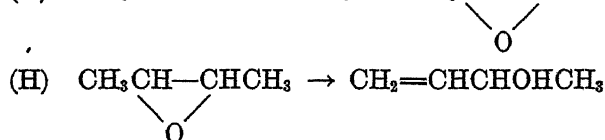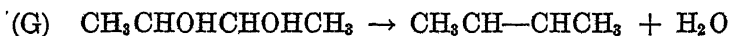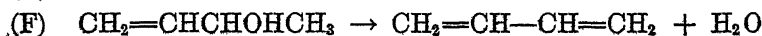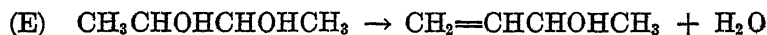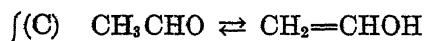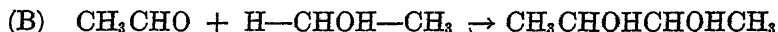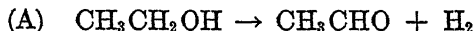
Reactions B and D utilize the keto and enol forms of ethanal, respectively. The final dehydration in all cases is that of 1-buten-3-ol. Since reactions A and B together require two molecular proportions of ethanol to form but one proportion each of 2,3-butanediol and hydrogen, it seems reasonable to include an

alternative pinaconic type of dehydrogenation to the butanediol rather than to ethanal:

$$(J) \quad 2CH_3CH_2OH \rightarrow 2CH_3\overset{\cdot}{C}H(OH) + 2\overset{\cdot}{H} \rightarrow$$
$$CH_3CH(OH):CH(OH)CH_3 + H:H$$
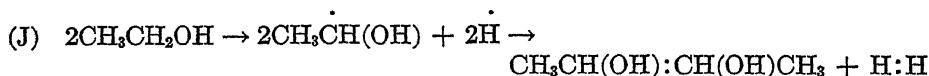
Finally, the authors consider the possibility of hemiacetal and acetal formation in the conversion of ethanol:

$$CH_3CH_2OH \rightarrow CH_3CHO + H_2$$

$$CH_3CHO + CH_3CH_2OH \rightleftarrows CH_3CH(OH)OC_2H_5$$

$$CH_3CH(OH)OC_2H_5 + CH_3CH_2OH \rightleftarrows CH_3CH(OC_2H_5)_2 + H_2O$$

Dehydration rather than reversion of the hemiacetal (i.e., ethyl α-hydroxy-ethyl ether) and a facile deëthanolation (128) of the true acetal would furnish ethyl vinyl ether:

$$CH_3CH(OH)OC_2H_5 \rightarrow CH_2{=}CHOC_2H_5 + H_2O$$

$$CH_3CH(OC_2H_5)_2 \rightarrow CH_2{=}CHOC_2H_5 + C_2H_5OH$$
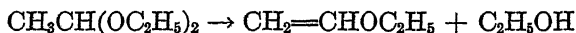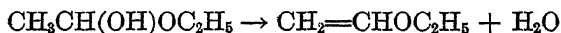
Cyclization of the ether would provide a chain of four methylene groups closed about the oxygen atom:

$$CH_2{=}CHOC_2H_5 \rightarrow \begin{array}{c} H_2C{\rule{1cm}{0.4pt}}CH_2 \\ | \qquad | \\ H_2C \qquad CH_2 \\ {\diagdown}\quad{\diagup} \\ O \end{array}$$
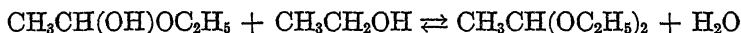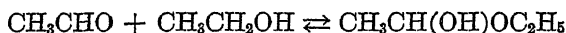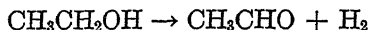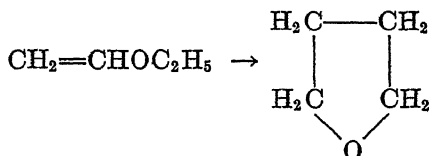
The 1,4-epoxybutane so formed would probably yield butadiene upon isomerization to and dehydration through a 1-buten-4-ol stage and also upon hydration to 1,4-butanediol, followed by an identical stage of dehydration:

$$\begin{array}{c} H_2C{\rule{1cm}{0.4pt}}CH_2 \\ | \qquad | \\ H_2C \qquad CH_2 \\ {\diagdown}\quad{\diagup} \\ O \end{array} \rightarrow CH_2{=}CHCH_2CH_2OH \xrightarrow{(-H_2O)} CH_2{=}CH{-}CH{=}CH_2$$

$$(+H_2O) \qquad (-H_2O)$$

$$CH_2OHCH_2CH_2CH_2OH$$
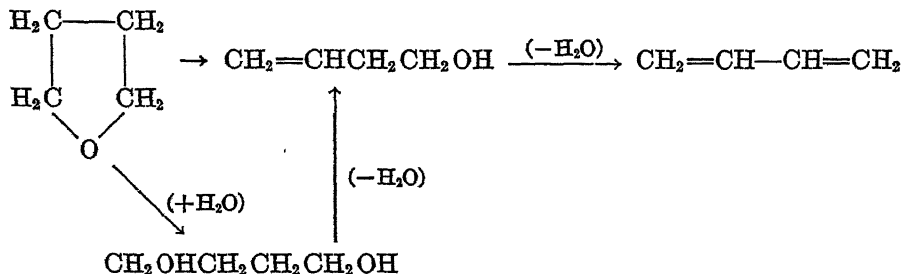
In lieu of cyclization, thermal scission of ethyl vinyl ether to form free vinyl radicals can be considered. Union of vinyl radicals through direct electronic coupling and conjugation of double bonds would yield butadiene, formerly called "divinyl":

$$2C\overset{\cdot}{H}_2{=}CH \rightarrow C\overset{\cdot}{H}_2{=}CH{-}CH{=}CH_2$$

Ipatieff demonstrated that ethanol forms butadiene over heated powdered aluminum (75, 76). At his suggestion, Gdanovitch continued the study of this reaction (39). The explanation finally accepted was formation of diethyl ether over the alumina coating always present on metallic aluminum, followed by conversion of ether into butadiene over the free metal (39, 74):

$$2C_2H_5OH \rightarrow C_2H_5OC_2H_5 + H_2O$$

$$C_2H_5OC_2H_5 \rightarrow CH_2{=}CH{-}CH{=}CH_2 + H_2 + H_2O$$
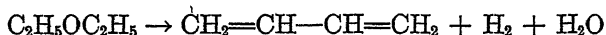
Filippov, also working under the direction of Ipatieff, investigated the aluminum-catalyzed reaction, finding that diethyl ether gives three times more butadiene than ethanol does (34).

Another theory is that of the dehydration of ethanol into ethene, catalytic dehydrogenation of the latter into ethyne, and subsequent interaction of both hydrocarbons:

$$CH_2{=}CH_2 + CH{\equiv}CH \rightarrow CH_2{=}CH{-}CH{=}CH_2$$

In favor of this series of reactions may be cited the presence of a catalyst having dehydrating and dehydrogenating components. Against it can be mentioned the lower yields of butadiene secured from ethene and ethyne mixtures under thermal, catalytic, or electrical conditions (22, 23). The oxidized character of the many by-products (82, 96, 97, 107) in Lebedev's reaction is also against the assumption of a transient conversion of ethanol or ethene into ethyne. Any formation of butadiene from ethene and ethyne via e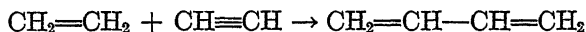thanol decomposition over Lebedev-type catalysts can be ascribed to particular reaction conditions. These could be induced by the presence of surplus dehydrogenating component in the catalyst or by excessive carbon deposition because of overheating.

Table 4 contains data on the direct conversion of ethanol into butadiene.

(c) Ostromyslenskiĭ's process

Ostromyslenskiĭ's process is the condensation of ethanol with ethanal:

$$C_2H_5OH + CH_3CHO \rightarrow CH_2{=}CH{-}CH{=}CH_2 + 2H_2O$$

Its discoverer stated (129) that the interaction of ethanol and ethanal proceeds by formation of a

"hydroxy ether under definite conditions and that this is followed by the formation of butanediol and crotyl alcohol [2-buten-1-ol]. The latter is finally converted into butadiene-1,2 by elimination of water, and isomerization of this diolefin under the action of catalysts results in formation of butadiene-1,3:

1. $CH_3CHO + C_2H_5OH \rightarrow CH_3CH(OH)OC_2H_5$

2. $CH_3CH(OH)OC_2H_5 \rightarrow CH_3CH(OH)CH_2CH_2(OH)$

3. $CH_3CH(OH)CH_2CH_2(OH) \rightarrow H_2O + CH_3CH{=}CHCH_2(OH)$

4. $CH_3CH{=}CHCH_2(OH) \rightarrow H_2O + CH_3CH{=}C{=}CH_2$

5. $CH_3CH{=}C{=}CH_2 \rightarrow CH_2{=}CHCH{=}CH_2$."

TABLE 4

Conversion of ethanol into butadiene

COMPOSITION OF FEED	APPARATUS AND CATALYST USED	TEMPERATURE °C.	PRESSURE atm.	REMARKS (B IS 1,3-BUTADIENE)	REFERENCES
Ethanol $2C_2H_5OH \rightarrow C_4H_6 + 2H_2O + H_2$	Catalyst: zinc and pumice	290–335 340–360	1 1	Yields of B were 0.12 and 0.145% by weight on feed at 290–335°C. and 340–360°C., respectively; the reactions were incomplete from the decomposition standpoint	(116)
	Catalyst: Al_2O_3	380		Yield of B was 0.0145% by weight on feed	(72)
	Glass tube charged with powdered aluminum	580–600 660–680		Yields of B were 0.85% by weight on feed	(74, 76)
	Catalyst: $Al_2O_3 + ZnO$			See patent for details; yield of B was "good"	(87)
	Catalyst: $Al_2O_3 + ZnO$	400	0.25	Yield of B was 18% by weight on feed	(86)
	The catalyst had two components (dehydrating and dehydrogenating)	. . . . .	. . . . .	See original article for details	(93)
	Quartz tube containing zinc dust and floridin	410		Yield of B was 15% by weight on feed	(92)
	Catalyst was probably $Al_2O_3 + ZnO$; pressure vessel used	Elevated		See patent for details	(90)
	Quartz tube containing ZnO + aluminum hydrosilicate $(Al_2O_3 \cdot SiO_2 \cdot xH_2O)$ as catalyst	410	1 or less	Yield of B was 15% by weight on fully decomposed ethanol; feed was 95% ethanol	(88)

Catalyst			Yield	Ref.
Catalyst of undisclosed composition			Yield of B was 20–25% by weight on product	(89)
Quartz tube (10 mm. diameter), or copper tube (28–30 mm. diameter), or copper tube (10 cm. diameter and 1 meter long), or enamelled iron tube (10 cm. diameter and 1 meter long), or copper (?) tube (12 cm. diameter and 3.5 meters long), or six tubes in parallel (copper ? or enamelled iron?) each 10 cm. diameter and 1 meter long; in each case a catalyst was used, but its composition was not revealed	440–450 (28–30 mm. Cu tube) 450 (3.5 meter tube)	0.934 (28–30 mm. Cu tube) 0.934–0.961 (six parallel tubes)	Yield of B from the "six tubes in parallel" was about 0.5 g. per liter of exit gas; article has much data on furnace construction and on mechanical recovery of B	(100)
Tubes of copper, iron, enamelled iron, aluminum-coated iron, or quartz; each tube contained two-component catalyst (one-component clay?)	435 (enamelled iron tube) 435–445 (copper or iron tube) 415–425 (aluminum-coated iron tube) 440 (quartz tube)	1 (iron, enamelled iron, or aluminum-coated iron tube) 0.974 (copper tube) 0.0395–0.526 (quartz tube)	Yield of B from copper tube was 20–23% by weight on fully decomposed ethanol; the enamelled iron tube gave a similar yield; yield of B from aluminum-coated iron tube was 20–22.4% by weight on fully decomposed ethanol; yield of B from plain iron tube was 15% by weight on fully decomposed ethanol; yield of B from quartz tube was 19.4% by weight on fully decomposed ethanol at 0.171 atmosphere pressure; article has data on and considers the significance of feed velocity coefficients, ethanol concentration, preheating of ethanol to reaction temperature, and absolute pressure	(99)

TABLE 4—Continued

COMPOSITION OF FEED	APPARATUS AND CATALYST USED	TEMPERATURE	PRESSURE	REMARKS (B IS 1,3-BUTADIENE)	REFERENCES
		°C.	atm.		
Ethanol $2C_2H_5OH \rightarrow C_4H_6 + 2H_2O + H_2$	Empty iron tube (case A), iron tube containing glass (case B), and copper tube packed with aluminum wire (case C)	600	1?	Yields of B were 0.06, 0.11, and 0.25% by weight on feed in cases A, B, and C, respectively	(99)
		About 425		No details of process available except on by-products	(167)
	Small laboratory furnace; catalyst was used, but its composition was not disclosed	450		With fresh catalyst, yield of B was 17.9% by weight on feed per pass and 22.3% by weight on fully decomposed feed; with fatigued catalyst, due to carbonization, yield of B was 11.2% by weight on feed per pass and 14.6% by weight on fully decomposed feed	(43)
	Large-scale laboratory unit; composition of catalyst not disclosed	450		With fatigued catalyst, due to repeated regeneration, yield of B was 6–7% by weight on feed per pass and 10–12% by weight on fully decomposed feed	(43)
	Copper tube, 1 meter long and 10 cm. in diameter, containing "well-selected" catalyst	450		Yield of B was over 20% by weight on fully decomposed feed; by-products include ethene, 2-butene, acetaldehyde, diethyl ether, butanol, and hexanol	(94)
	Composition of catalyst not disclosed; probably oxides	450	0.974–0.987	Yield of B was 16% by weight on feed per pass and 24% by weight on fully decomposed feed	(95)

|					
Ethanol and alkanol diluents $2C_2H_5OH \rightarrow C_4H_6 + 2H_2O + H_2$	Silica tube, 1 meter long, in cases A, B, and C; six tubes (copper or enamelled iron) in parallel, each 1 meter long, in case D; diluents were methanol in cases A and B, 2-propanol in case C, and 1-propanol in case D; in all cases the composition of the catalyst was not disclosed, but the dehydrating and dehydrogenating components were 25% and 75%, respectively	425 (case A) 450 (case B) 460 (case C) 450–455 (case D)	0.961–0.974 (all cases)	Yields of B were 1.74, 2.17, 15.2, and 25.15% by weight on absolute ethanol feed per pass in cases A, B, C, and D, respectively	(83)
	Probably a 1-meter copper tube; the catalyst had two components (one component clay?)	435–445?	1	Yield of B was 17.7% by weight on absolute ethanol feed per pass and 25.1% by weight on fully decomposed absolute ethanol feed	(99)
Ethanol and steam $2C_2H_5OH \rightarrow C_4H_6 + 2H_2O + H_2$	"Laboratory furnace"; feed mixture was "54% by volume ethanol" in cases A and B, "76% by volume ethanol" in cases C and D, and "94.5% by volume ethanol" in cases E and F; catalyst had two components (one component clay?)	440 (cases A, C, E) 500 (cases B, D, F)	1 (all cases)	Yields of B were 15.0, 18.8, 15.3–16.5, 18.0–19.3, 24.0, and 17.7% by weight on fully decomposed absolute ethanol feed in cases A, B, C, D, E, and F, respectively	(99)

Some of the supposed intermediary products (ethyl α-hydroxyethyl ether and 1,2-butadiene) were isolated; the others were believed to be involved because of their conversion into butadiene in separate reactions. The given set of equations is partly inconsistent with the following statements of Ostromyslenskiï (129):

In the general fate of the initial substances in the reaction under discussion, ethyl hydroxyethyl ether plays, apparently, no part. The reaction occurs at 360–440°, while the hydroxyether is easily decomposed on heating into aldehyde and alcohol, especially in the presence of water. . . . Thus, hydroxyether exists only during a short period of time and again virtually completely decomposes into its components. The first phase of the process is a reversible reaction:

$$CH_3CHO + C_2H_5OH \rightleftarrows CH_3CH(OH)OC_2H_5$$
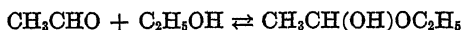
It occurs under definite conditions on mixing acetaldehyde and ethyl alcohol and is apparently not a necessary step in the process.

Butadiene-1,3 is actually obtained from the mixture of ethyl alcohol and acetaldehyde and not from the hydroxyether. It was found by experiment that acetaldehyde and ethyl alcohol may be charged into the reaction zone at high temperatures (360–440°) independently of each other and in the presence of water and, furthermore, that acetaldehyde may be substituted by paraldehyde. In all these cases, the reaction produces under identical conditions the same yield of butadiene-1,3 although formation of hydroxyether is entirely prevented. Decomposition of hydroxyether at high reaction temperatures (360–440°) into acetaldehyde and ethyl alcohol is accompanied by condensation of these substances through carbon atoms. Concerning the question which of the carbon atoms of the components are involved in the union, aldehyde possesses an ability to enter into different reactions and add an almost limitless number of different substances in different condensations. All these reactions are due to the aldehyde group —CHO, the carbon atom of which is without exception the most mobile and active. The aldehyde group is rearranged as follows:

$$R-C\diagdown\diagup O \quad\to\quad R-C\diagdown\diagup O-H$$
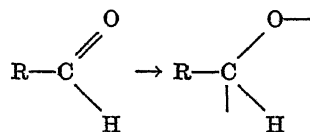
The two free bonds determine the effect of each reaction. In rare cases, aldehydes react by their tautomeric form of unsaturated alcohols:

$$RCH_2CH{=}O \rightleftarrows RCH{=}CH(OH)$$
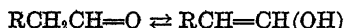
However, in these condensations, only the carbon atom of the aldehyde group is actively involved in the reaction. For this reason, it is beyond doubt that in the reaction described by the present author, condensation also occurs through the carbon atom of this group. The rearrangement of acetaldehyde in the condensation may be described by:

$$CH_3CHO \to CH_3C\diagdown\diagup O- \qquad ; \quad or \quad CH_3CHO \to CH_2{=}CH(OH).$$
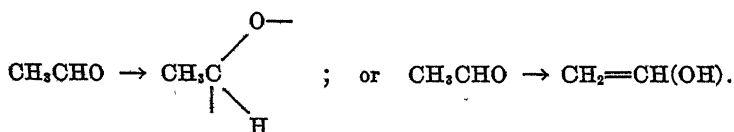
Concerning the carbon atom of ethyl alcohol participating in the union of the molecules, the author succeeded in definitely solving this question by substitution of ethyl alcohol by

one of its homologs, namely, isopropyl alcohol. . . . Experiments showed that a mixture of isopropyl alcohol and acetaldehyde gives under ordinary reaction conditions exclusively pentadiene-1,3 and in good yields (6)[1]. Among the by-products of the reaction, not even traces of isoprene or dimethylallene were found. This interesting fact directly indicates that condensation of alcohols and aldehydes involves union of the carbon atom of the alde-hyde group with the carbon atom of the methyl group of the alcohols. Consequently, formation of butadiene-1,3 in the author's reaction occurs either through butanediol-1,3 or buten-1-ol-4:

1. $CH_3CHO + CH_3CH_2(OH) \rightarrow CH_3CH(OH)CH_2CH_2(OH)$; or

2. $CH_2\!\!=\!\!CH(OH) + CH_3CH_2(OH) \rightarrow CH_2\!\!=\!\!CHCH_2CH_2(OH)$.
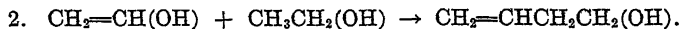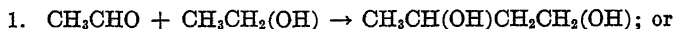
It will be shown later that in this reaction, butadiene-1,3 is formed by isomerization of methylallene; buten-1-ol-4 can give upon dehydration only butadiene-1,3 but not methyl-allene

$$CH_2\!\!=\!\!CHCH_2CH_2(OH) \rightarrow H_2O + CH_2\!\!=\!\!CHCH\!\!=\!\!CH_2.$$

The reaction 2 is therefore impossible. Condensation of acetaldehyde and ethyl alcohol occurs, consequently, through butanediol.

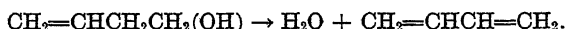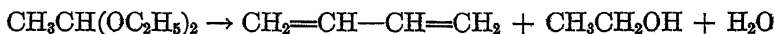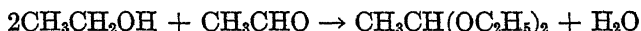Ostromyslenskiĭ and Kelbasinskiĭ postulated a union of ethanol and ethanal to form 1,3-butanediol and 2-buten-1-ol, but admitted the possibility of acetal formation leading to production of butadiene as follows (143):

$$2CH_3CH_2OH + CH_3CHO \rightarrow CH_3CH(OC_2H_5)_2 + H_2O$$

$$CH_3CH(OC_2H_5)_2 \rightarrow CH_2\!\!=\!\!CH\!\!-\!\!CH\!\!=\!\!CH_2 + CH_3CH_2OH + H_2O$$

Lebedev (89) regarded Ostromyslenskiĭ's reaction, or the direct condensation of ethanol and ethanal, as a synthesis of butadiene similar to his own process, because ethanal can be regarded as a product in ethanol conversion. Lebedev's last experiments (95) demonstrated that the addition of 10 and 20 per cent of ethene by weight to ethanol affects the amount of butadiene formed to only an insignificant extent. Ethene was evidently very slightly activated on the sur-face of the particular catalyst used in these tests. However, ethanal in admix-ture with ethanol participated extensively in the formation of butadiene.

Our discussion of Ostromyslenskiĭ's process begins with a consideration of his statement that the condensation of ethanol and ethanal proceeds through a butanediol. The constitution of this butanediol was formulated *a priori* as 1,3-butanediol from *Zaĭtsev's rule* (182): the requisite hydrogen atom is split off from the least hydrogenated carbon atom. Because hydroxyl groups split off more easily from secondary than from primary alcohol groups, it follows that the 3-position hydroxyl group and one of the 2-position hydrogen atoms would be eliminated as water.

Ostromyslenskiĭ further assumed that 1,3-butanediol does not split off two molecules of water simultaneously. Intermediary formation of 2-buten-1-ol was given as the first of two dehydrations. 1,2-Butadiene was taken as the final dehydration product, since some was isolated by the expedient of reacting ethanol and ethanal over pure alumina. It gave butadiene when subsequently

[1] Reference 144 in this paper.

isomerized over impure grades of the same catalyst. In summarizing his own study, Ostromyslenskiĭ formulated (129) a second group of five equations almost identical with the first set (page 73). The second equation of the second group, however, appears to be meaningless:

2a. $CH_3CHO + C_2H_5OH + CH_3CH(OH)OC_2H_5 \rightarrow$
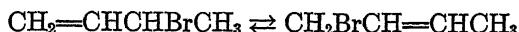
$$2CH_3CHOHCH_2CH_2OH$$
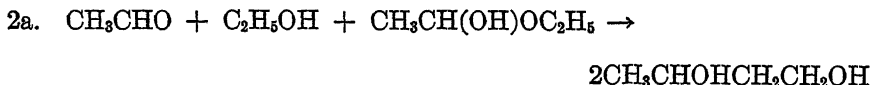
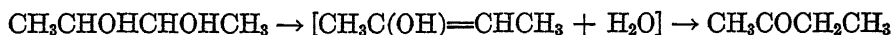Ostromyslenskiĭ failed to state which set of equations was most plausible.

This picture of Ostromyslenskiĭ's process is complicated somewhat by the possibility that at high temperatures 1-buten-3-ol and 2-buten-1-ol may exhibit an interconversion, in the known manner (44, 45, 181) of 3-bromo-1-butene and 1-bromo-2-butene:

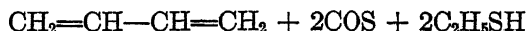$$CH_2\!\!=\!\!CHCHBrCH_3 \rightleftarrows CH_2BrCH\!\!=\!\!CHCH_3$$

Butadiene has been obtained by individual dehydrations of 1-buten-3-ol, 1-buten-4-ol, and 2-buten-1-ol over catalysts at temperatures probably low enough to avoid significant interconversion. 1-Buten-3-ol yielded butadiene at 140°C. in the presence of trichloroacetic acid (154). 1-Buten-4-ol was similarly dehydrated at 270–290°C. over a fused mixture of ammonium and potassium alums (59). 2-Buten-1-ol gave butadiene at 140–160°C. over toluidine bisulfate (30). These three dehydrations would proceed rapidly at the high temperatures, 360–440°C., used in the ethanol and ethanal condensation. Kinetic studies could establish which of the butenols at the given temperatures is the most stable, probably 2-buten-1-ol, or the most reactive, e.g., 1-buten-3-ol or 1-buten-4-ol.

Ostromyslenskiĭ's proposition that 1,3-butanediol is an intermediary product rests on firmer ground: related reaction conditions and catalysts for the conversion of this diol into butadiene were already known (84, 109, 134). The dehydration of 1,3-butanediol has been repeatedly studied since 1915, the year of Ostromyslenskiĭ's publication, though not from the instructive standpoint of the kinetics of reaction. 1,3-Butanediol apparently has never been isolated from the reaction products of either an ethanol plus ethanal (129) or an ethanol per se (89) condensation. Its presence among the products of the latter type of condensation was inferred from the isolation of 2-buten-1-ol, but one must remember that the last compound is readily obtainable by hydrogenation (9, 106) of 2-butenal from the dehydration of 3-hydroxybutanal. From this point of view, 2-buten-1-ol is a product of the catalytic treatment of ethanal per se rather than of ethanol reacting with ethanal. There are several indications that 2,3-butanediol can be the precursor of butadiene. One is the established occurrence (89) of 2-butanone and the probable presence (89) of 2,3-butanedione among the products of the catalytic condensation of ethanol per se. Another is the formation of 2,3-butanediol and traces of 2,3-butanedione when a mixture of ethanol and ethanal is exposed to sunlight (14, 146). Dehydration of 2,3-butanediol

into butadiene (48) is competitive with formation of 2-butanone (5, 15, 48, 172):

$$CH_3CHOHCHOHCH_3 \rightarrow CH_2=CH-CH=CH_2 + 2H_2O$$

$$CH_3CHOHCHOHCH_3 \rightarrow [CH_3C(OH)=CHCH_3 + H_2O] \rightarrow CH_3COCH_2CH_3$$

Moreover, derivatives of 2,3-butanediol, such as the diformate (53) and the diacetate (53, 126), and a 2,3-butanedithiol derivative (149) having the structure of 2,3-butene bis(ethylxanthogenic acid) yield butadiene upon decomposition:

$$CH_3CH(O-CO-H)CH(O-CO-H)CH_3 \rightarrow$$
$$CH_2=CH-CH=CH_2 + CO + CO_2 + H_2 + H_2O$$

$$CH_3CH(O-CO-CH_3)CH(O-CO-CH_3)CH_3 \rightarrow$$
$$CH_2=CH-CH=CH_2 + 2CH_3COOH$$

$$CH_3CH(S-CS-OC_2H_5)CH(S-CS-OC_2H_5)CH_3 \rightarrow$$
$$CH_2=CH-CH=CH_2 + 2COS + 2C_2H_5SH$$
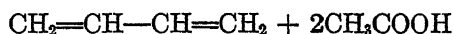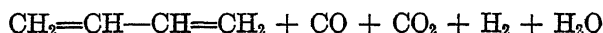
(d) Other ethanol condensations

Paraldehyde can replace part or all of the ethanal in an ethanol condensation (129, 141). It is a trimer of ethanal and presumably would depolymerize prior to reacting with ethanol. The course of the conversion is probably as follows:

$$(C_2H_4O)_3 \rightarrow 3C_2H_4O$$

$$\underline{C_2H_5OH + C_2H_4O \rightarrow CH_2=CH-CH=CH_2 + 2H_2O}$$

$$3C_2H_5OH + (C_2H_4O)_3 \rightarrow 3CH_2=CH-CH=CH_2 + 6H_2O$$
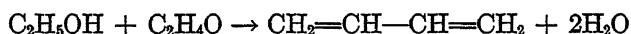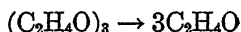
1,2-Ethanediol likewise can replace ethanal in Ostromyslenskiĭ's reaction (6). This substitution is expected because of the thermal conversion of this diol into ethanal. However, a conversion proceeding via 1,3- or 1,4-butanediol is to be considered also:

$$CH_2OHCH_2OH + CH_2OHCH_3 \rightarrow CH_2OHCH_2CHOHCH_3 + H_2O$$

$$CH_2OHCH_2OH + CH_3CH_2OH \rightarrow CH_2OHCH_2CH_2CH_2OH + H_2O$$
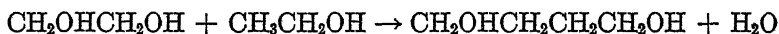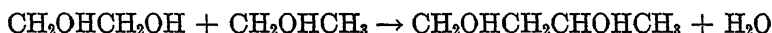
A mixture of ethanol and ethyne is reported (65) to give butadiene, but this reaction can be questioned on grounds similar to those discounting an ethanol and ethene conversion. Any formation of butadiene would be ascribable to a more appropriate ethanol *per se* condensation, to a hydration of ethyne into ethanal, which then reacts with ethanol, or to dehydration of ethanol into ethene prior to a Berthelot condensation between ethene and ethyne. The over-all reaction, of course, in the last two cases is:

$$C_2H_5OH + CH\equiv CH \rightarrow CH_2=CH-CH=CH_2 + H_2O$$

TABLE 5

Condensation of ethanol with close derivatives

COMPOSITION OF FEED	APPARATUS AND CATALYST USED	TEMPERATURE °C.	PRESSURE atm.	REMARKS (B IS 1,3-BUTADIENE)	REFERENCES
Ethanol and ethanal $C_2H_5OH + CH_3CHO \rightarrow C_4H_6 + 2H_2O$	Catalyst: Al_2O_3	440-460	0.895-0.934	Yield of B was 14% by weight on total feed; steam used?; data for 97 experiments given	(143)
	Catalyst: Al_2O_3	360-450		Yield of B = ?	(126)
	Catalysts were red phosphorus; glacial H_3PO_4; sulfanilic acid; $BaCl_2$; or Al_2O_3 ("argilla pura")	360-440		Yields of B = ?	(129)
	Catalyst was used, but its composition was not disclosed	450	0.974-0.987	Yield of B was 9.5% by weight on total feed and 11% by weight on fully decomposed feed; feed used was ethanol and ethanal in equal amounts by weight	(95)
	Special unit of the plant "Krasnyi Bogatyr" in Moscow during 1919-1922			Yield of B was 6% by weight on feed	(94)
	Catalyst was $Al_2(SO_4)_3 \cdot 12H_2O$; feed mixture was ethanol 54, ethanal 33.5, and water 12.5 parts by weight	320-360	1	Yield of B was 19.8% by weight on ethanol and ethanal feed	(78)
	Catalyst was $Al_2(SO_4)_3$ on pumice; feed mixture was ethanol 47, ethanal 23, and water 30 parts by weight	320-360?	1?	Yield of B = ?	(78)
	Catalyst: basic aluminum sulfate	?	1?	Yield of B = ?	(78)

Ethanol, ethanal, and paraldehyde $3C_2H_5OH + (C_2H_4O)_3 \rightarrow 3C_4H_6 + 6H_2O$	Catalyst: Al_2O_3	440–460	Yield of B = ?	(141)
Ethanol and paraldehyde $3C_2H_5OH + (C_2H_4O)_3 \rightarrow 3C_4H_6 + 6H_2O$			Yield of B = ?	(129)
Ethanol and 1,1-dibromoethane $C_2H_5OH + CHBr_2CH_3 \rightarrow C_4H_6 + H_2O + 2HBr$	Catalyst was used, but its composition was not disclosed		Yield of B = ?	(126)
Ethanol and 1,2-dibromoethane $C_2H_5OH + CH_2BrCH_2Br \rightarrow C_4H_6 + H_2O + 2HBr$	Catalyst: $Al_2O_3 + BaCl_2$	400	Yield of B = ?	(129)
	Catalyst was used, but its composition was not disclosed		Yield of B was "poor"	(126)
Ethanol and bromoethene (vinyl bromide) $C_2H_5OH + CH_2{=}CHBr \rightarrow C_4H_6 + H_2O + HBr$	Catalyst: $Al_2O_3 + BaCl_2$	400	Yield of B = ?	(129)
Ethanol and ethyne $C_2H_5OH + CH{\equiv}CH \rightarrow C_4H_6 + H_2O$	Catalyst was used, but its composition was not disclosed	>350	Yield of B = ?	(65)
Ethanol and 1,2-ethanediol (ethylene glycol) $C_2H_5OH + CH_2OHCH_2OH \rightarrow C_4H_6 + 3H_2O$	Catalyst: Al_2O_3 or aluminum silicate or floridin	350–450	Yield of B = ?	(6)

Table 5 contains data on condensations of ethanol with close derivatives, including ethanal.

(e) Higher alkanols

2-Propanol, upon passage over pumice (117) at 615–620°C. or through a hard glass tube (71) at 840–850°C., yields small amounts of butadiene. One may assume that two molecules of 2-propanol upon dehydration form propene and eventually two vinyl and two methyl radicals. Also it is possible that another molecule furnishes acetone and the equivalent of two free hydrogen atoms (Ḣ), which allow the methyl radicals to be removed as methane. The over-all effect, applicable to the relatively few molecules converted and irrespective of any union of vinyl radicals and atomic hydrogen to form ethene, would then be:

$$3CH_3CHOHCH_3 \rightarrow CH_2\!\!=\!\!CH\!\!-\!\!CH\!\!=\!\!CH_2 + H_2O + CH_4 + CH_3COCH_3$$

Both 1- and 2-butanol can be converted into butadiene either thermally or catalytically. A mixed alumina and chromia catalyst converts 1-butanol into considerable amounts of butadiene at 575–625°C. and an absolute pressure of 150–128 mm. of mercury (81). Partial oxidation of "butanol" also yields butadiene (33).

1-Butanol undergoes dehydration and dehydrogenation in forming butadiene:

$$CH_2OHCH_2CH_2CH_3 \rightarrow CH_2\!\!=\!\!CH\!\!-\!\!CH\!\!=\!\!CH_2 + H_2O + H_2$$
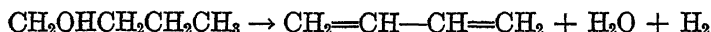
Dehydration presumably precedes dehydrogenation, so that 1-butene rather than 1-buten-4-ol would be the principal intermediate. Questions of (a) an isomerization of 1-butene into 2-butene following dehydration of 1-butanol, and (b) which alkene is dehydrogenated, are left open. This much is certain: the temperatures used in the conversion (32, 81, 149, 169) of 1-butanol into butadiene are considerably higher than those for the isomerization (25) of 1-butene into 2-butene.

2-Butanol, like 1-butanol, undergoes dehydration and dehydrogenation into butadiene (32, 83):

$$CH_3CHOHCH_2CH_3 \rightarrow CH_2\!\!=\!\!CH\!\!-\!\!CH\!\!=\!\!CH_2 + H_2O + H_2$$
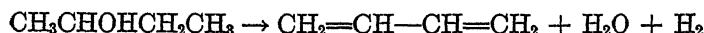
Again assuming the validity of prior dehydration and of Zaïtsev's rule governing its course, the intermediate product would be cis- or trans-2-butene. A 1,4-dehydrogenation of 2-butene would then yield butadiene.

"Butanol" oxidations probably involve competitive initial dehydration and hydroxylation:

$$C_4H_9OH \begin{array}{c} \nearrow \quad C_4H_8 + H_2O \\ \\ \searrow \quad C_4H_8(OH)_2 \end{array} \quad \begin{array}{c} \searrow \tfrac{1}{2}O_2 \\ \\ \nearrow \end{array} \quad C_4H_7OH + H_2O \rightarrow C_4H_6 + 2H_2O$$
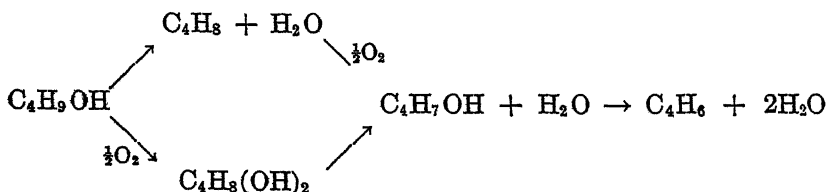
In the 1-butanol case, assuming oxidation in the β-position to the hydroxymethyl group, the intermediates would be 1-butene, 1,3-butanediol, 1-buten-3-ol, 1-buten-4-ol, and 2-buten-1-ol. Those for 2-butanol, assuming oxidation in the α-position to the hydroxymethylene group, would be 1- and 2-butenes, 2,3-butanediol, 1-buten-3-ol, and 2-buten-1-ol.

Only a trace of butadiene is formed when 2-methyl-1-propanol is passed over pumice at 600–610°C. under atmospheric pressure (119). The principal products are hydrogen, water, carbon monoxide, methane, ethane, ethene, propene, "butene," ethanal, propanal, and 2-methylpropanal.

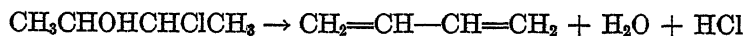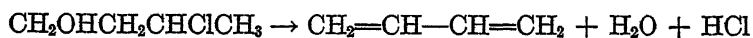Partial oxidation of "pentanol" yields butadiene (33). A great number of formulations for the partial oxidation of "pentanol" are possible. These depend upon (a) the several orders in which hydroxyl groups can be subtracted or added, (b) the number of hydroxyl groups accumulating in a molecule before dehydrations, (c) the "promptness" with which the terminal methyl groups of 1-, 2-, and 3-pentanols become hydroxymethyl, aldehyde (formyl), and carboxyl groups, (d) the isomerization of intermediary products, and (e) the operation of 1-, 2-, 3-, or 4-hydroxylation. The latter operations are hydroxylations of a carbon atom in the 1-, 2-, 3-, or 4-position to an existing hydroxymethylene, hydroxymethyl, formyl, carboxyl, or 1-alken-1-yl group. A possibility of dehydrogenation without intermediary hydroxylation is a matter of speculation; its existence could be determined only with difficulty. If the velocity of partial oxidation approaches that of rapid combustion or explosion, newly formed hydroxyl radicals cannot become localized about carbon atoms. Upon cooling of the products, definite hydroxy compounds would develop. Their isolation obviously would not solve the question of direct *versus* indirect dehydrogenation at higher temperatures. Another question concerns the extent of demethylation, which would convert pentanols into hydroxybutyls and butenols:

$$C_5H_{11}OH \rightarrow C_4H_8OH + CH_3 \rightarrow C_4H_7OH + H + CH_3$$
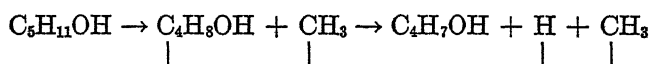
Its operation would be favored by the low activation energy for a carbon–carbon bond scission, but would be extensively superseded by exothermic hydroxylations with or without dehydration of new hydroxyls.

Both 3-methyl-1-butanol and 2-methyl-2-butanol undergo conversions into butadiene over pumice at 600°C., though with small yields (120, 121). Thermal treatment of 3-methyl-1-butanol also yields small amounts of butadiene (7, 71, 130, 169, 171).

At high temperatures over a catalyst, 3-chloro-1-butanol and 3-chloro-2-butanol undergo dehydration and dehydrodechlorination (68, 110):

$$CH_2OHCH_2CHClCH_3 \rightarrow CH_2{=}CH{-}CH{=}CH_2 + H_2O + HCl$$

$$CH_3CHOHCHClCH_3 \rightarrow CH_2{=}CH{-}CH{=}CH_2 + H_2O + HCl$$

The two elimination processes, i.e., formation of water and of hydrogen chloride, are favored by the increase in strengths of the 1,2- and 3,4-carbon–carbon linkages and of the C—OH bond in the reactants compared with the H—OH bond

TABLE 6

Conversion of higher alkanols (C_3H_7OH and above) into butadiene

PROCESS AND ALKANOL USED	APPARATUS AND CATALYSTS USED	TEMPERATURE	PRESSURE	REMARKS (B IS 1,3-BUTADIENE)	REFERENCES
		°C.	atm.		
Catalysis of 2-propanol (isopropyl alcohol) Probably $3CH_3CHOHCH_3 \rightarrow C_4H_6 + CH_3COCH_3 + 2CH_4 + 2H_2O$	Catalyst: pumice	615–620	1	Yield of B was 0.054% by weight on feed	(117)
	Hard glass tube	840–850	1?	Yield of B = ? (low in value)	(71)
Catalysis of 2-methyl-1-propanol (iso-butyl alcohol) Probably $CH_3CH(CH_3)CH_2OH \rightarrow C_4H_6 + H_2O + H_2$	Catalyst: pumice	600–610	1	Yield of B was 0.022% by weight on feed	(119)
	Catalyst: mixture of aluminum silicate and reduced copper	Red heat	In vacuo unless diluents used	Yield of B = ?	(149)
	Quartz tube	Red heat	1	Yield of B was 11% by weight on feed; if desired, Al_2O_3 or kieselguhr may be used as catalyst	(32)
Dehydration and dehydrogenation of 1-butanol $C_4H_9OH \rightarrow C_4H_6 + H_2O + H_2$		750	1	Yield of B was 0.41% by weight on feed	(169)
				Yield of B was 1.2–4.8% by weight on gaseous hydrocarbons produced	(124)
	Quartz tube containing a 4% Cr_2O_3 and 96% Al_2O_3 catalyst	575 (Expt. 1) 600 (Expt. 2) 625 (Expt. 3)	0.197 (Expt. 1) 0.175 (Expt. 2) 0.168 (Expt. 3)	Yields of B were 1.8, 5.1, and 7.4% by weight on feed in experiments 1, 2, and 3, respectively	(81)

Dehydration and dehydrogenation of 2-butanol $C_4H_9OH \rightarrow C_4H_6 + H_2O + H_2$	Quartz tube	Red heat	1	Yield of B was 14.6% by weight on feed; if desired, Al_2O_3 or kieselguhr may be used as catalyst	(32)
	Quartz tube containing 5% of a dehydrating catalyst and 95% of a dehydrogenating catalyst; components of the catalyst not disclosed	440	0.961–0.974	Yield of B was 0.9% by weight on feed per pass and 1.06% by weight on fully decomposed feed	(83)
Partial oxidation (by air) of "butanol" vaporized by illuminating gas $C_4H_9OH + \frac{1}{2}O_2 \rightarrow C_4H_6 + 2H_2O$		?	1	Yield of B = ?	(33)
Partial oxidation (by air) of "pentanol" vaporized by illuminating gas $C_5H_{11}OH + O_2 \rightarrow C_4H_6 + CO_2 + H_2O$	Burner tube was heated to prevent condensation of pentanol vapors	?	1	Yield of B = ?	(33)
	Porcelain tube	Red heat	1	Yield of B = ?	(7)
	Iron tube	Medium red heat	1	Yield of B = ?	(171)
Dehydration and demethanation of 3-methyl-1-butanol $CH_2OHCH_2CH(CH_3)CH_3 \rightarrow C_4H_6 + H_2O + CH_4$	Catalyst: pumice	580–620	1	Yield of B was 0.18% by weight on feed	(120)
	Iron tube	660–680?	1?	Yield of B = ?	(71)
		750	1	Yield of B was 0.725% by weight on feed	(169)
		500–600	1		(130)

TABLE 6—*Continued*

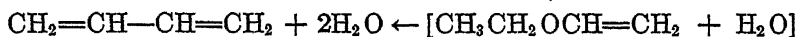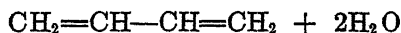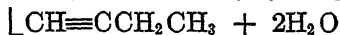| PROCESS AND ALKANOL USED	APPARATUS AND CATALYSTS USED	TEMPERATURE °C.	PRESSURE atm.	REMARKS (B IS 1,3-BUTADIENE)	REFERENCES
Dehydration and demethanation of 2-methyl-2-butanol $(CH_3)_2C(OH)CH_2CH_3 \rightarrow C_4H_6 + H_2O + CH_4$	Catalyst: pumice	600–620	1	Yield of B was 0.071% by weight on feed	(121)
Dehydration and dehydrodechlorination of 3-chloro-1-butanol $CH_2OHCH_2CHClCH_3 \rightarrow C_4H_6 + H_2O + HCl$	Catalyst: Al_2O_3, $BaCl_2$, or TiO_2	High	1 or *in vacuo*		(68)
Dehydration and dehydrodechlorination of 3-chloro-2-butanol $CH_3CHOHCHClCH_3 \rightarrow C_4H_6 + H_2O + HCl$	Catalyst: H_3PO_4 (?) on pumice	Over 400	1 or *in vacuo*	Yield of B = ?	(110)

in the product. Dehydration should precede dehydrodechlorination, since water has the higher heat of formation in these reactions. These statements and others on heat of reaction values are based on Pauling's bond energies (147), which are: C—C, 58.6, C=C, 100; C≡C, 123; C—H, 87.3; C—O, 70.0; C=O in CH_2O, 142; C=O in RCHO, 149; C=O in R_2CO, 152; C—I, 45.5; C—Cl, 66.5; H—H, 103.4; O—H, 110.2 kcal. per an Avogadro number of bonds, and on 5.0 kcal. resonance energy per gram-mole of butadiene. When passed over magnesium chloride at 350°C., with or without steam, or at 300°C. over anhydrous magnesium sulfate, 3-chloro-2-butanol forms much more 2-butanone than butadiene (48). These catalysts evidently favor dehydrodechlorination rather than dehydration.

When distilled at an absolute pressure of 16 mm. of mercury, 4-chloro-1-butanol liberates hydrogen chloride and probably forms 1,4-epoxybutane (3, 80). Consequently, butadiene formation by decomposition of the epoxybutane seems possible at higher temperatures.

Table 6 contains data on conversions of 2-propanol and higher alkanols into butadiene.

2. Alkanediols

1,2-Ethanediol has not been reported as a direct source of butadiene. However, according to a Russian patent (6), it condenses with ethene or ethanol to form butadiene. The condensation with ethene is explicable on several bases. One explanation developed by the present authors is alkylation to 1,2-butanediol or ethyl β-hydroxyethyl ether, followed by dehydration:

$$CH_2OHCH_2OH + CH_2=CH_2 \rightarrow CH_2OHCHOHCH_2CH_3$$

$$CH_2OHCHOHCH_2CH_3 \rightarrow$$

$$\begin{cases} ^-CH_2OHCH=CHCH_3 + H_2O^\cdot \\ CH_2=C=CHCH_3 + 2H_2O \qquad CH_2=CH—CH=CH_2 + 2H_2O \\ CH≡CCH_2CH_3 + 2H_2O \end{cases}$$

$$CH_2OHCH_2OH + CH_2=CH_2 \rightarrow CH_3CH_2OCH_2CH_2OH$$
$$\downarrow$$
$$CH_2=CH—CH=CH_2 + 2H_2O \leftarrow [CH_3CH_2OCH=CH_2 + H_2O]$$

Another explanation depends upon a probable transformation of the ethanediol into ethenol, i.e., vinyl alcohol, and its stabilization product, ethanal. Hydration of ethene into ethanol by water from ethanediol introduces Ostromyslenskiĭ's condensation:

$$CH_3CH_2OH + CH_3CHO \rightarrow CH_2=CH—CH=CH_2 + 2H_2O$$

whereas further dehydration of ethenol to form ethyne brings Berthelot's reaction into the picture:

$$CH_2=CH_2 + CH≡CH \rightarrow CH_2=CH—CH=CH_2$$
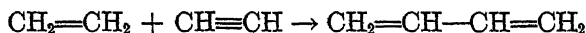
Condensation of ethanal into 3-hydroxybutanal or of ethene into 1- or 2-butene, requiring subsequent reduction (24) of 3-hydroxybutanal and dehydrogenation of the butenes, respectively, are still other mechanisms. Reduction conditions of sufficient potential would probably prevail in the presence of (a) atomic hydrogen traceable to ethene decomposition, (b) ethanol from ethene hydration or ethanal hydrogenation, or (c) ethanal decomposition products, e.g., carbon monoxide plus methane mixture. Dehydrogenation of 1- and 2-butenes would be accelerated by the presence of hydrogen acceptors, including keto compounds and alkenes.
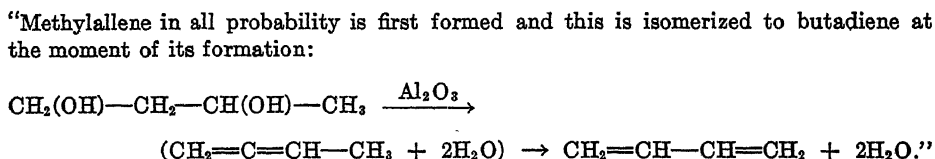
The catalytic bidehydration of 1,3-butanediol is conducted advantageously under reduced pressure (166). Numerous catalysts are available (47, 50, 58, 66, 67, 84, 109, 115, 129, 130, 134, 152, 162, 166, 178). The course of dehydration of 1,3-butanediol probably involves intermediary formation of 1-buten-3-ol, 1-buten-4-ol, 2-buten-1-ol, or 1,3-epoxybutane. Ostromyslenskiĭ's view of the reaction was (135):

"Methylallene in all probability is first formed and this is isomerized to butadiene at the moment of its formation:

$$CH_2(OH)—CH_2—CH(OH)—CH_3 \xrightarrow{Al_2O_3}$$

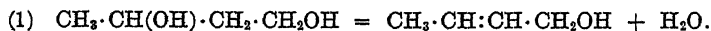$$(CH_2{=}C{=}CH—CH_3 + 2H_2O) \rightarrow CH_2{=}CH—CH{=}CH_2 + 2H_2O.\text{"}$$

This viewpoint was discounted in our discussions on Lebedev's ethanol process and on Ostromyslenskiĭ's ethanol and ethanal juncture. A bond-energy analysis of the over-all reaction,

$$CH_2OHCH_2CHOHCH_3 \rightarrow CH_2{=}CH—CH{=}CH_2 + 2H_2O$$

indicates that its thermal energy requirements, 6.5 kcal. per gram-mole of diol, are very low and practically that of an ordinary alkanol dehydration (5.7 kcal.). This low endothermicity for a bidehydration is due to the usual 5.0 kcal. calorific contribution in the establishment of electronic resonance among butadiene structures. Kyriakides committed himself in part to the following explanation (84):

"The dehydration of 1,3-glycols to hydrocarbons of the divinyl series, would seem to proceed according to the following course:

(1) $CH_3 \cdot CH(OH) \cdot CH_2 \cdot CH_2OH = CH_3 \cdot CH{:}CH \cdot CH_2OH + H_2O.$

(2) $CH_3 \cdot CH{:}CH \cdot CH_2OH = CH_2{:}CH \cdot CH{:}CH_2 + H_2O.$

R. B. Earle [Kyriakides' colleague] has been able to isolate crotonyl alcohol, $CH_3CH{:}CHCH_2OH$, among the decomposition products in the formation of divinyl. In fact, β-butylene glycol [1,3-butanediol], if submitted to the action of catalysts at temperatures not exceeding 350°, seems to be dehydrated principally to butenol. The assumption that crotonyl alcohol is an intermediate step in the complete dehydration of the glycol is supported by the discovery that buten-2-ol-1 itself, is readily dehydrated to butadiene-1,3, if subjected to the pyrogenetic action of catalysts. Charon[1] [reference 10 of this paper], furthermore, states that, by heating the bromo-ester of the unsaturated alcohol with potassium formate at 160–180°, he obtained the *diene* as the principal product of the reaction. The dehalogenation of bromo-1-butene-2 to divinyl is explained by Charon on the

assumption that methylallene, $CH_3 \cdot CH:C:CH_2$, is the primary reduction product. This substance, however, is immediately isomerized to the more symmetrically constituted divinyl under the influence of the high temperature, the symmetrical configurations being the stablest of all."

1,4-Butanediol produces butadiene when catalytically dehydrated over acidic substances, such as acid phosphates, silicic acid, phosphotungstic acid, phosphomolybdic acid, or boric acid (64). 2,3-Butanediol yields both butadiene and 2-butanone when dehydrated over either magnesium chloride or magnesium sulfate (48).

Mechanisms of the conversion of 1,4-butanediol and 2,3-butanediol have been considered under Lebedev's process. The suggested intermediates are 1-buten-4-ol and 1,4-epoxybutane for the first diol, but 2,3-epoxybutane and/or 1-buten-3-ol for the second diol. Ring strain in 2,3-epoxybutane would hinder its formation and so decrease its stability as to favor production of 1-buten-3-ol (or 3-butanol-1,2-diyl) from the corresponding but-2-yl-3-oxyl:
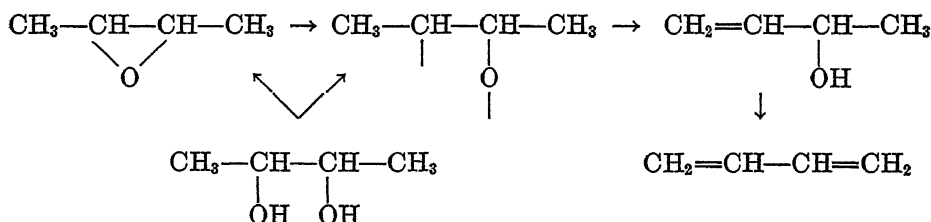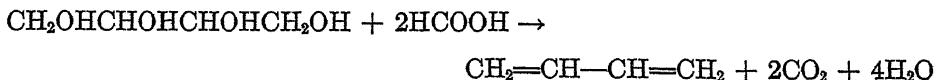
$$CH_3{-}\underset{\underset{O}{\diagdown\diagup}}{CH}{-}CH{-}CH_3 \;\rightarrow\; CH_3{-}\underset{\underset{\underset{|}{O}}{|}}{CH}{-}\underset{|}{CH}{-}CH_3 \;\rightarrow\; CH_2{=}CH{-}\underset{\underset{OH}{|}}{CH}{-}CH_3$$

$$\diagdown\diagup \qquad\qquad\qquad\qquad\qquad\qquad\qquad \downarrow$$

$$CH_3{-}\underset{\underset{OH}{|}}{CH}{-}\underset{\underset{OH}{|}}{CH}{-}CH_3 \qquad\qquad CH_2{=}CH{-}CH{=}CH_2$$

Table 7 contains data on the conversion of butanediols into butadiene.

3. Alkanetetrol

Reduction of 1,2,3,4-butanetetrol by formic acid at temperatures of 100°C. to 230°C. yields butadiene, as illustrated by the following equation (13, 52, 156, 175):

$$CH_2OHCHOHCHOHCH_2OH + 2HCOOH \rightarrow$$
$$CH_2{=}CH{-}CH{=}CH_2 + 2CO_2 + 4H_2O$$

Erythrol monoformin, $CH_2{=}CHCHOHCH_2OCHO$, is also formed (156). Its structure is such that it should yield butadiene through formation of water and carbon dioxide. One may assume that 1,2,3,4-butanetetrol diformate is also an intermediate product, for it yields butadiene at 210–220°C. (51):

$$C_4H_6(OH)_2(OCHO)_2 \rightarrow C_4H_6 + 2CO_2 + 2H_2O$$
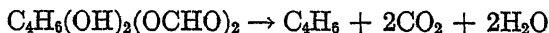
4. Alkenols

1-Propen-3-ol, upon contact with brass at 600°C., yields propenal, hydrogen, carbon monoxide, methane, propene, and butadiene (71, 73).

1-Buten-3-ol dehydrates to butadiene when heated in the presence of trichloroacetic acid, phosphorus pentoxide, or precipitated alumina (154):

$$CH_2{=}CHCHOHCH_3 \rightarrow CH_2{=}CH{-}CH{=}CH_2 + H_2O$$

TABLE 7

Conversion of butanediols and of butanetetrol into butadiene

PROCESS AND STARTING DERIVATIVE	APPARATUS AND CATALYST USED	TEMPERATURE °C.	PRESSURE atm.	REMARKS (B IS 1,3-BUTADIENE)	REFERENCES
Dehydration of 1,3-butanediol CH_2OHCH_2CHOH- $CH_3 \rightarrow C_4H_6 + 2H_2O$	Catalyst: H_3PO_4 on pumice	Heated	*In vacuo* if desired	Yield of B = ?; by-products can be recycled	(109)
	Catalyst: ignited kaolin	380–400	1	Yield of B was about 5.5% by weight on feed	(84)
				Yield of B was 50–65% (probably on the theoretical, which is 60.0%)	(130)
	Catalysts: Al_2O_3; red phosphorus; glacial H_3PO_4; sulfanilic acid	350–480		Yield of B = ?	(129, 134)
	Catalysts: Al_2O_3; caustic alkali; H_3PO_4; oxalic acid; $KHSO_4$	450–470 (Al_2O_3 or caustic alkali) 300–350 (H_3PO_4)		Yields of B were 36–45% by weight on feed	(152)
	Catalyst: 1% of red phosphorus on pumice	300–330		Yield of B was 39–42% by weight on feed	(67)
	Catalyst: NaH_2PO_4 + red phosphorus	300–330		Yield of B was 80% on the product	(67)
	Catalyst: NaH_2PO_4 + H_3PO_4 on graphite	260	1?	Yield of B = ?	(58)
	Catalyst: $Ca(H_2PO_4)_2$ + H_3PO_4 on lampblack and graphite	260	1?	Yield of B = ?	(58)

Vaporizer for feed mixture of butanediol and water; catalyst was potassium aluminum sulfate predehydrated at 150–180°C.	240–250	1?	Yield of B was 48% by weight on absolute butanediol feed per pass	(66)
Vaporizer for feed mixture of butanediol and water; catalyst was mixture of potassium aluminum sulfate and ammonium aluminum sulfate premixed and predehydrated at 180°C. in stream of nitrogen	270–290	1?	Yield of B was 48–49% by weight on absolute butanediol feed	(66)
Catalyst: $AlPO_4 + H_3PO_4$	450	1	Yield of B was 40% by weight on feed	(166)
Catalyst: $AlPO_4 + H_3PO_4$	450	0.25	Yield of B was 52% by weight on feed	(166)
Catalyst was $AlPO_4 + H_3PO_4$; steam and a 17% solution of the butanediol in water used	450?	1	Yield of B was 45% by weight on absolute butanediol feed	(166)
A "complex aluminum phosphate dehydration catalyst" was used in the presence of steam	285	1?	Yield of B was 42–48% by weight on feed without recycling and 54–57% by weight on butanediol with recycling of 1-buten-4-ol, which is a by-product	(178
Catalyst was H_2SO_4 (1%) in water; an autoclave was used	200	>15	Yield of B was 48% by weight on feed	(50)
Quartz tube containing the following catalysts: Al_2O_3 from $Al(NO_3)_3 + NH_4OH$ (expts. 1–3)	250 (expts. 1, 4, 7, 12, 15, 18, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51)	0.034 (all cases)	Yields of B were 4.3, 8.9, 10.6, 4.8, 19.4, 18.1, 8.5, 10.5, 13.3, 14.0, 20.5, 26.8, 27.0, 22.8, 12.0, 20.4, 21.2, 17.0, 26.2, 29.0, 33.8,	(115)

TABLE 7—Continued

PROCESS AND STARTING DERIVATIVE	APPARATUS AND CATALYST USED	TEMPERATURE	PRESSURE	REMARKS (B is 1,3-BUTADIENE)	REFERENCES
		°C.	atm.		
Dehydration of 1,3-butanediol CH_2OHCH_2CHOH-$CH_3 \rightarrow C_4H_6 + 2H_2O$	Al_2O_3 from $NaAlO_2 + CO_2$ (expts. 4-6)	300 (expts. 2, 5, 8, 10, 13, 16, 19, 25, 28, 31, 34, 37, 40, 43, 46, 49, 52, 57)		35.1, 37.0, 6.8, 15.9, 16.2, 5.9, 13.7, 14.2, 17.8, 24 6, 23.6, 30.6, 28.6, 23.6, 21.1, 23.9, 25.8, 11.0, 21.0, 18.6, 20.6, 30.4, 29.4, 31.7, 40.1, 31.4, 12.8, 20.1, 19.1, 17.6, 23.0, 24.3, 2.5, 24.0, 22.3, 6.8, and 16.5% by weight on feed for experiments 1-58, respectively	
	SiO_2 gel (expts. 7-9)				
	Kaolin (Nippon Yakkyokuho) (expts. 10-11)				
	Kaolin (Korea) (expts. 12-14)	350 (expts. 3, 6, 9, 11, 14, 17, 20, 26, 29, 32, 35, 38, 41, 44, 47, 50, 53, 54, 55, 58)			
	Japanese acid clay (Itoigawa). (expts. 15-17)				
	Kaolin (50 parts) + P_2O_5 (50 parts) (expts. 18-23)				
	Kaolin (50 parts) + Al_2O_3 (50 parts) (expts. 24-26)	400 (expts. 21, 56)			
	Kaolin (49 parts) + Al_2O_3 (49 parts) + KOH (2 parts) (expts. 27-29)	450 (expt. 22)			
	Kaolin (50 parts) + Japanese acid clay (50 parts) (expts. 30-32)	500 (expt. 23)			
	Kaolin (50 parts) + $FeSO_4$ (50 parts) (expts. 33-35)				
	Kaolin (94 parts) + Fe_2O_3 (6 parts) (expts. 36-38)				
	Kaolin (80 parts) + Fe_2O_3 (20 parts) (expts. 39-41)				
	Kaolin (94.7 parts) + Fe_2O_3 (5 parts) + KOH (0.3 part) (expts. 42-44)				
	Kaolin (94 parts) + Fe_2O_3 (5 parts) + KOH (1 part) (expts. 45-47)				
	Kaolin (92 parts) + Fe_2O_3 (5 parts) + KOH (3 parts) (expts. 48-50)				

Kaolin (94 parts) + Ni(OH)$_2$ (5 parts) + KOH (1 part) (expts. 51–53) "Red mud" (i.e., clay after removal of Al$_2$O$_3$ with soda lime) (expt. 54) CaSO$_4$ (expts. 55–56) AlPO$_4$ (expts. 57–58)					
	Catalyst: triethyl phosphate	300–350	1	Yield of B was 48.6% by weight on feed	(47)
	Catalyst was POCl$_3$; pumice or charcoal was used for heat transfer purposes	300–350	1	Yield of B was 45.9% by weight on feed	(47)
	Catalyst was NaH$_2$PO$_4$ + H$_3$PO$_4$ + graphite; steam and n-hexane used as diluents	250	1?	Yield of B was 51% by weight on feed	(162)
	Steam and benzene used as diluents; catalyst was H$_3$PO$_4$ on graphite (prepared at 160 °C. from sodium phosphate solution, primary n-butylamine phosphate, and graphite)	280	1?	Yield of B was 54% by weight on feed	(162)
Dehydration of 2:1 mixture of 1,3-butanediol and 1,4-butanediol in presence of steam and 1,4-epoxybutane C$_4$H$_{10}$O$_2$ → C$_4$H$_6$ + 2H$_2$O	Catalyst: NaH$_2$PO$_4$ + H$_3$PO$_4$ on graphite	260	1?	Yield of B was 54% by weight on C$_4$H$_{10}$O$_2$ feed	(162)

TABLE 7—Continued

| PROCESS AND STARTING DERIVATIVE	APPARATUS AND CATALYST USED	TEMPERATURE °C.	PRESSURE atm.	REMARKS (B IS 1,3-BUTADIENE)	REFERENCES
Dehydration of 1,4-butanediol CH_2OHCH_2- $CH_2CH_2OH \rightarrow$ $C_4H_6 + 2H_2O$	Catalyst of acid character, such as NaH_2PO_4, $CaHPO_4$, $Ca(H_2PO_4)_2$, Cu_2O, tungsten oxide, molybdenum oxide, silicic acid, phosphotungstic acid, phosphomolybdic acid, or boric acid			See patent for details	(64)
	Catalyst was NaH_2PO_4; steam and 1,4-epoxybutane used as diluents	280	1?	Yield of B was 57% by weight on $C_4H_{10}O_2$ feed	(162)
Dehydration of 2,3-butanediol $CH_3CHOHCH$- $OHCH_3 \rightarrow$ $C_4H_6 + 2H_2O$	Catalysts: $MgSO_4$; $MgCl_2$; $MgCl_2$ + steam	300–320 (first catalyst) 350 (second and third catalysts)		Yields of B were 1.60, 2.48, and 1.77% by weight on feed for first, second, and third catalysts, respectively	(48)
	Vapor-phase catalytic process	?	?	Yield of B = ?	(114)
Reduction of 1,2, 3,4-butanetetrol (erythrite) $CH_2OHCHOH$- $CHOHCH_2OH$ $+ 2HCOOH \rightarrow$ $C_4H_6 + 2CO_2$ $+ 4H_2O$		230		Yield of B = ?	(52)
		Distillation	1	Yield of B = ?	(13)
		> 100	1	Yield of B was 6.67% by weight on butanetetrol	(156)
		130–150	1	Yield of B = ?	(175)

Isomerization of 1-buten-3-ol into 2-buten-1-ol may occur initially. An incomplete isomerization to 2-buten-1-ol occurs upon prolonged boiling with dilute hydrochloric acid (154). Trichloroacetins may be intermediates when trichloroacetic acid is used as a dehydration catalyst.
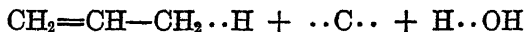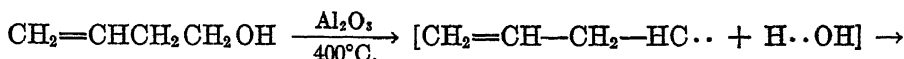
1-Buten-4-ol undergoes dehydration to butadiene when heated with a fused mixture of ammonium and potassium alums or with acid phosphates or pyrophosphates (59):

$$CH_2{=}CHCH_2CH_2OH \rightarrow CH_2{=}CH{-}CH{=}CH_2 + H_2O$$

Alumina as catalyst leads to formation of much more propene and carbon than butadiene. This phenomenon was ascribed to a facile elimination and decomposition of formaldehyde (19):

$$CH_2{=}CHCH_2CH_2OH \rightarrow [CH_2{=}CHCH_3 + CH_2O] \rightarrow$$

$$CH_2{=}CHCH_3 + C + H_2O$$
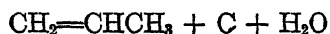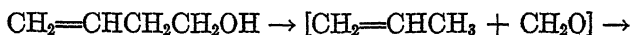
The present authors suggest that, because of a balanced electronic state of carbon atom 4 and with excessive activity of alumina, the desired 3,4-dehydration is partly replaced by an undesired 4,4-dehydration:

$$CH_2{=}CHCH_2\,CH_2\,OH \xrightarrow[400°C.]{Al_2O_3} [CH_2{=}CH{-}CH_2{-}HC\cdot\cdot + H\cdot\cdot OH] \rightarrow$$

$$CH_2{=}CH{-}CH_2\cdot\cdot H + \cdot\cdot C\cdot\cdot + H\cdot\cdot OH$$

Adsorption of water molecules on the alumina at temperatures around 400°C. is probably strong enough to prevent rehydration of carbon atoms to form formaldehyde. As a consequence, the carbon lattice would be formed.

2-Buten-1-ol forms butadiene when heated with toluidine bisulfate, anhydrous oxalic acid, phosphoric acid, phosphorus oxychloride, alumina, aluminum chloride, aluminum phosphate, or kaolin (30, 47, 84):

$$CH_2OHCH{=}CHCH_3 \rightarrow CH_2{=}CH{-}CH{=}CH_2 + H_2O$$

If 1,4 loss of water occurs in one step, then the energy-rich *cis*-form of 2-buten-1-ol yields *cis*-butadiene, which enters into equilibrium (113, 158, 159) with the *trans*-alkadiene:
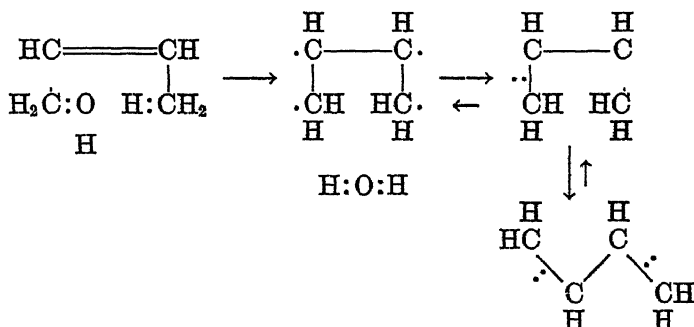
TABLE 8

*Conversion of alkenols and alkenediols into butadiene*

PROCESS AND STARTING DERIVATIVE	APPARATUS, CATALYSTS, AND SPECIAL REACTANTS	TEMPERATURE °C.	PRESSURE atm.	REMARKS (B IS 1,3-BUTADIENE)	REFERENCES
Catalytic treatment of 1-propen-3-ol (allyl alcohol) Probably $2CH_2{=}CHCH_2OH \rightarrow C_4H_6 + 2CO + 3H_2$	Brass tube containing brass shavings	600	1?	Yield of B = ? (low in value)	(71)
Dehydration of 1-buten-3-ol (methylvinylcarbinol) $CH_2{=}CHCHOHCH_3 \rightarrow C_4H_6 + H_2O$	Catalyst of undisclosed composition			Yield of B = ?	(157)
	Catalyst of undisclosed composition	360		Yield of B was about 45-55% on feed per pass and about 56-79% on fully decomposed feed	(156)
	Catalyst: trichloroacetic acid	140		Yield of B = ?; product also had two isomeric monoesters	(154)
	Phosphorus pentoxide was used as reactant			Yield of B was slightly above 15% on feed	(154)
Dehydration of 1-buten-3-ol and/or 2-buten-1-ol Probably $CH_2{=}CHCHOHCH_3 \rightarrow C_4H_6 + H_2O$	Catalyst: precipitated Al_2O_3	265	1	Yield of B was 20% on feed; Al_2O_3 precipitated on sodium aluminate and placed among layers of pumice was used as catalyst also, but yield of B = ? in this case	(154)

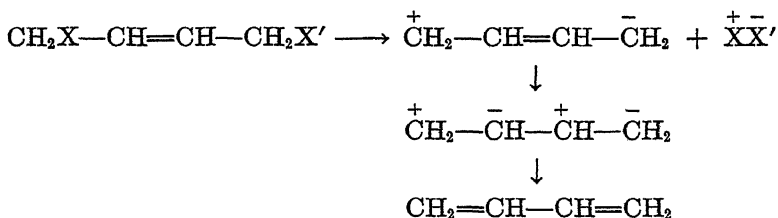| Reaction	Catalyst / Notes	Temperature		Remarks	Ref.
Dehydration of 1-buten-4-ol (allyl carbinol) $CH_2=CHCH_2CH_2OH \rightarrow C_4H_6 + H_2O$	Catalyst was prepared by dehydrating and fusing a mixture of ammonium alum (90%) and potash alum (10%)	270–290	1?	Yield of B was 63.7–67.5% by weight on feed, using one recycle; acid phosphates or pyrophosphates also had a catalytic effect	(59)
	Catalyst: Al_2O_3	400–405	1?	Yield of B was 2.25% by weight on feed	(19)
Dehydration of 2-buten-1-ol (crotyl alcohol) $CH_2OHCH=CHCH_3 \rightarrow C_4H_6 + H_2O$	Toluidine bisulfate, anhydrous oxalic acid, $KHSO_4$, H_3PO_4, Al_2O_3, and $AlCl_3$ were catalysts named	140–160 (first catalyst) "Warmed" (second catalyst)	1	Yield of B was 22.5–30% by weight on feed for first catalyst and 30–37.5% by weight on feed for second catalyst; yield of B = ? for other catalysts	(30)
	Catalyst: probably kaolin or $AlPO_4$	400–450	1?	Yield of B = ?	(84)
	$POCl_3$ (?) was used as reactant	300–350?	1	Yield of B was 32% (?) by weight on feed	(47)
Dehydroxylation of 1-butene-3,4-diol (erythrol) $CH_2=CHCHOHCH_2OH + 2Cu \rightarrow C_4H_6 + H_2O + Cu_2O$	Copper was used as reactant	280	1	Yield of B was 0.193% by weight on butenediol feed	(176)

For the given structural formulation, an over-all heat of reaction amounting to about 0.3 kcal. exothermic can be computed on the basis of $+1.0$, -5.7, and $+5.0$ kcal., respectively, for available *cis* energy of butenol, heat of simple dehydration, and butadiene resonance energy.

Prévost listed dehydration of 2-buten-1-ol among a group of 1,4-eliminations in which a 2,3 double bond opens to form two conjugated double bonds (153). Two interpretations of the 1,4-eliminations were submitted:

1. Migration of a substituent from carbon atom 4 to carbon atom 2, for example, could give a 3-alkene. This upon loss of adjacent groups in the 1- and 2-positions would form a 1,2 double bond conjugated with the 3,4 double bond:

$$CH_2X—CH=CH—CH_2X' \longrightarrow CH_2X—CHX'—CH=CH_2$$
$$\downarrow$$
$$CH_2=CH—CH=CH_2 + XX'$$
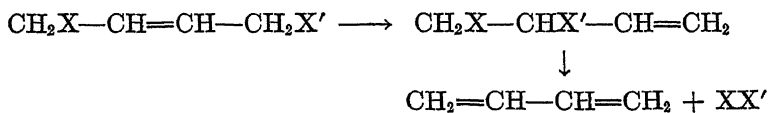
2. Elimination of oppositely charged substituents from carbon atoms 1 and 4 could give $\overset{+}{C}H_2—CH=CH—\overset{-}{C}H_2$, whose double bond would open simultaneously to form $\overset{+}{C}H_2—\overset{-}{C}H—\overset{+}{C}H—\overset{-}{C}H_2$, which is a highly activated state of butadiene:

$$CH_2X—CH=CH—CH_2X' \longrightarrow \overset{+}{C}H_2—CH=CH—\overset{-}{C}H_2 + \overset{+}{X}\overset{-}{X'}$$
$$\downarrow$$
$$\overset{+}{C}H_2—\overset{-}{C}H—\overset{+}{C}H—\overset{-}{C}H_2$$
$$\downarrow$$
$$CH_2=CH—CH=CH_2$$

Interpretation 1 suggests the following course for the dehydration:

$$CH_2OHCH=CHCH_3 \longrightarrow CH_2=CHCHOHCH_3$$
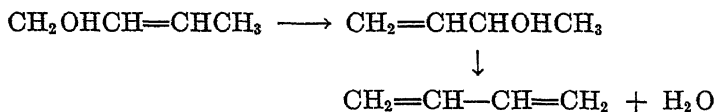$$\downarrow$$
$$CH_2=CH—CH=CH_2 + H_2O$$

Table 8 contains data on the conversion of alkenols into butadiene.

5. Alkenediol

1-Butene-3,4-diol forms butadiene, propanal, 2-butenal, 2-keto-1-butanol, 3,4-hexanedione, carbon dioxide, and water when heated at 280°C. with copper (175). These products are indicative of extensive electronic changes among butenediol molecules. Urion, investigator of the butenediol conversion, considered butadiene to be formed by a scission of both hydroxyl groups:

$$CH_2=CHCHOHCH_2OH \xrightarrow{\text{Cu}} CH_2=CH—CH=CH_2 + 2\overset{.}{O}H$$
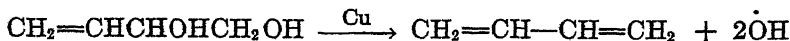
Nothing was stated regarding further reactions of the hydroxyl groups. A union of two vinyl fragments was also mentioned. The presence of 2-butenal, i.e., C_4H_6O, as a dehydration plus isomerization product suggests the possibility of its reduction to butadiene. If the latter reaction occurs, it indicates a reductive action of copper comparable with that of zinc in organic synthesis.
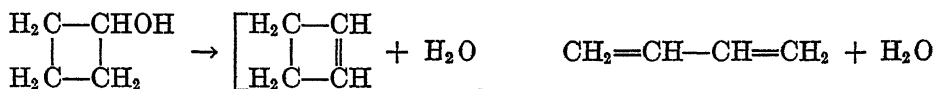
B. CYCLIC MEMBERS

1. Cyclanyl alkanol

Cyclopropylcarbinol undergoes a complicated decomposition at 300–400°C. in the presence of alumina (19). The products include much propene, very little butene, butadiene, besides 1-buten-4-ol, 3-butenal, cyclobutanol, cyclobutanone, carbon, carbon monoxide, hydrogen, and water. Formation of propene, carbon, and water was considered to be the main reaction. Butadiene forms instead of methylenecyclopropane, which is the expected dehydration product (19, 20). 1-Buten-4-ol and cyclobutanol are obviously isomerization products, which upon dehydrogenation would yield 3-butenal and cyclobutanone, respectively.
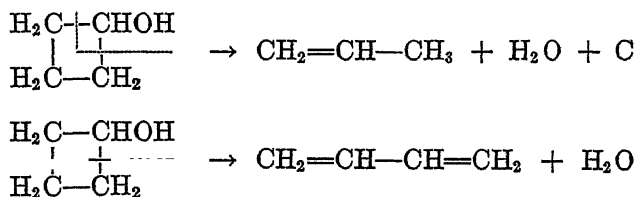
2. Cyclanols

Cyclanols generally give high yields of butadiene. This fact recalls the analogous behavior of cyclohexane, cyclohexene, and benzene, in which resonance among valence-bond structures plays an important rôle.

The conversion of cyclobutanol into butadiene was reported by Ostromyslenskiĭ to occur quantitatively at 300–350°C. over alumina (126, 131):

$$\begin{matrix} H_2C—CHOH \\ |\quad\quad| \\ H_2C—CH_2 \end{matrix} \rightarrow \begin{bmatrix} H_2C—CH \\ |\quad\quad\| \\ H_2C—CH \end{bmatrix} + H_2O \qquad CH_2{=}CH—CH{=}CH_2 + H_2O$$
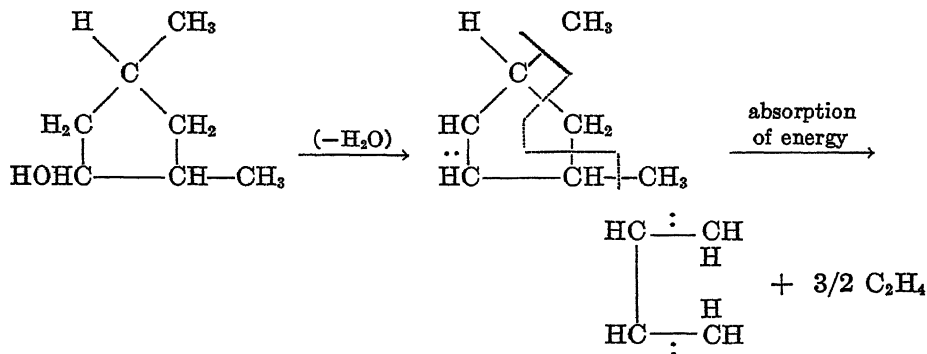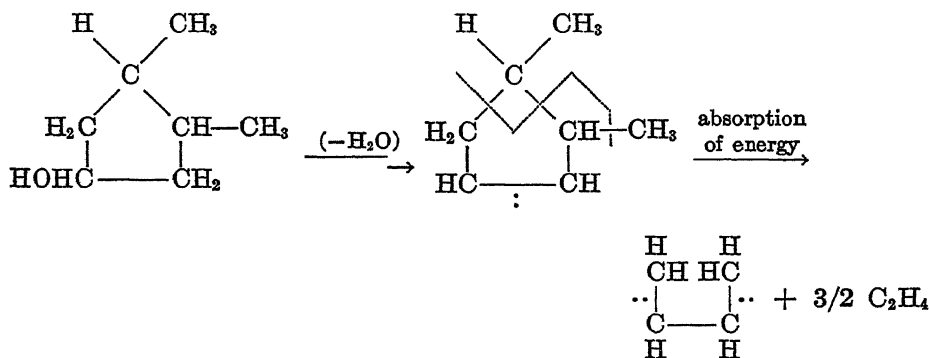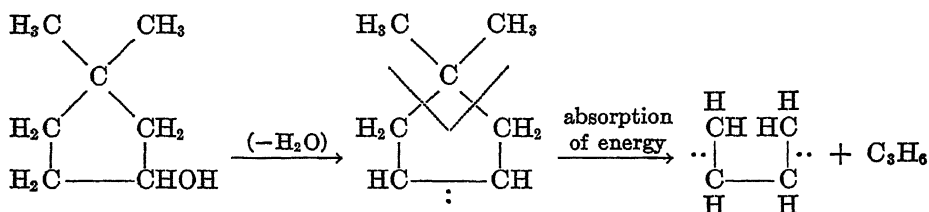
Cyclobutene was assumed to be the intermediate responsible for the reaction. Doyarenko, however, found that the products formed at 360–390°C. included propene, butadiene, cyclobutanone, 2-butenal, carbon, and water (19). "Dehydrations" to propene and butadiene were considered to be the main reactions:

$$\begin{matrix} H_2C{-}|{-}CHOH \\ |\quad\quad| \\ H_2C—CH_2 \end{matrix} \rightarrow CH_2{=}CH—CH_3 + H_2O + C$$

$$\begin{matrix} H_2C—CHOH \\ |\quad\quad| \\ H_2C—CH_2 \end{matrix} \rightarrow CH_2{=}CH—CH{=}CH_2 + H_2O$$

The conversion mechanism was assumed to be formation of unstable, highly energized molecules immediately upon dehydration, such that sufficient excess energy would be present to break a C—C or open a C=C linkage (19, 20).

When passed through a copper tube containing an inner silver gauze at a dark red heat, 1-methyl-3-cyclopentanol and "dimethylcyclopentanols" undergo dehydration and ring scission (29). These conversions into butadiene were not

further described, but probably involve formation of ethene and propene as by-products. The present authors suggest that the following reactions occur:

$$\text{(reaction 1)} \xrightarrow{(-H_2O)} \xrightarrow[\text{of energy}]{\text{absorption}} \cdots + C_2H_4$$

$$\text{(reaction 2)} \xrightarrow{(-H_2O)} \xrightarrow[\text{of energy}]{\text{absorption}} \cdots + C_3H_6$$

$$\text{(reaction 3)} \xrightarrow{(-H_2O)} \xrightarrow[\text{of energy}]{\text{absorption}} \cdots + 3/2\ C_2H_4$$

$$\text{(reaction 4)} \xrightarrow{(-H_2O)} \xrightarrow[\text{of energy}]{\text{absorption}} \cdots + 3/2\ C_2H_4$$
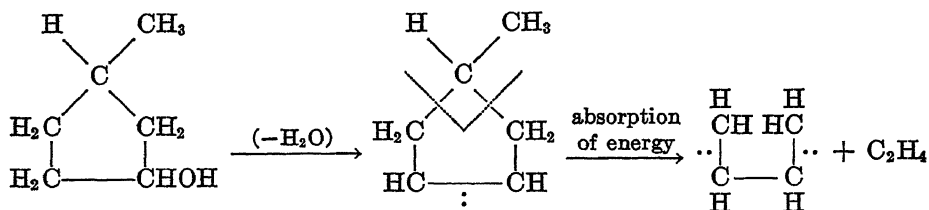
All of the processes given are over-all endothermic. An absorption of external energy occurs in (a) dehydration with double-bond formation, (b) the transformation of two $\overset{\mid}{C}H$—CH_3 into two $\overset{\mid}{C}H_2$ groups plus CH_2=CH_2, and (c) the conver-

sions of

$$\text{two}\ \ \begin{matrix}-CH_2\\ |\\ CH_2\\ |\\ -CH_2\end{matrix}\text{, one}\ \ \begin{matrix}-CH_2\\ |\\ CH-CH_3\\ |\\ -CH_2\end{matrix}\text{, or one}\ \ \begin{matrix}-CH_2\\ |\\ C(CH_3)_2\\ |\\ -CH_2\end{matrix}$$
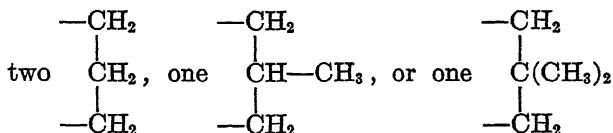
into $CH_2{=}CH_2$ (or $CH_2{=}CH-CH_3$) and into the two methylene terminals characteristic of activated butadiene.

Cyclohexanol gives considerable amounts of ethene and butadiene when passed through tubes of quartz, platinum, silver, or (less favorably) of iron or porcelain, heated to redness (26, 27, 28, 54):
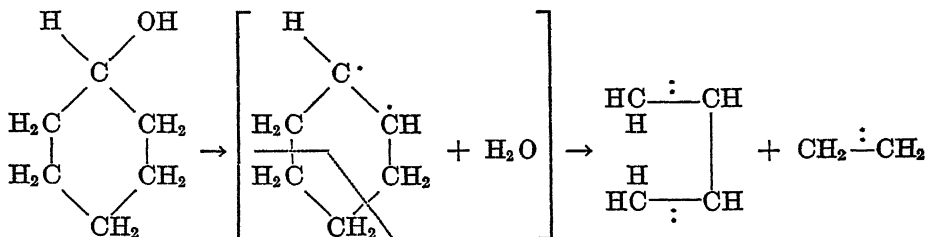
The *cis*-butadiene, of course, would immediately form a large proportion of the *trans*-modification.

3. Hydroxybenzene (phenol)

Hydroxybenzene forms hydrogen, carbon, carbon monoxide, carbon dioxide, methane, ethene, ethyne, butadiene, benzene, naphthalene, anthracene, phenanthrene, and chrysene when conducted with nitrogen at 650–750°C. over pumice (49). A direct formation of butadiene from hydroxybenzene seems possible:
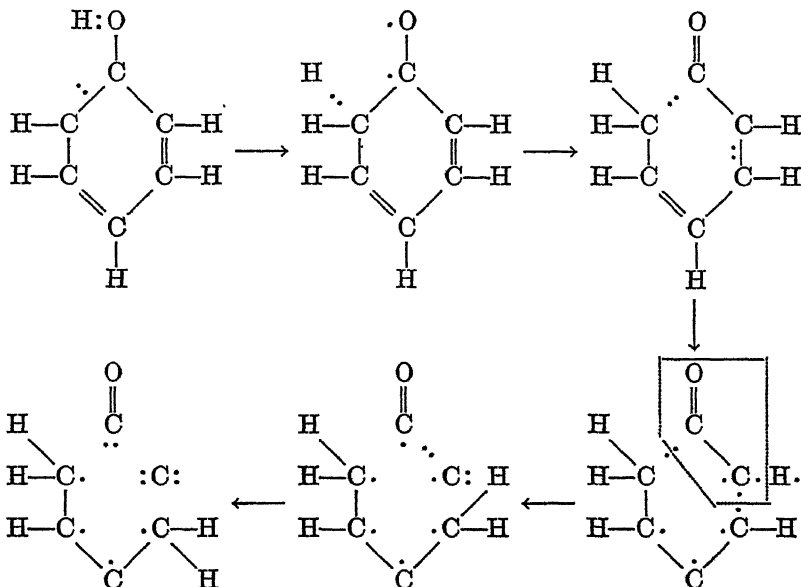
An alternative two-step formulation ending with a similar electronic inter-
pretation is the disproportionation of hydroxybenzene into benzene and the
easily convertible 1,2- and 1,4-dihydroxybenzenes. Pumice might exert a
splitting action toward the hydroxyl group even at temperatures below 750°C.,
in which case water should have been formed. Hydroxybenzene also could com-
bine with hydrogen atoms to form cyclohexanol, which dehydrates into cyclo-
hexene and further decomposes into ethene and butadiene.

4. Dihydroxybenzenes

When 1,2-dihydroxybenzene is passed with nitrogen over glass rings at 550°C.,
large amounts of butadiene and carbon monoxide are produced (49). The
assigned course of the reaction was:

$$C_6H_4(OH)_2 \rightarrow [2CO + 2H + C_4H_4] \rightarrow CH_2{=}CH{-}CH{=}CH_2 + 2CO$$
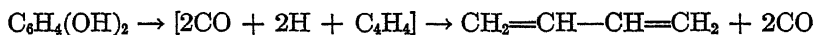
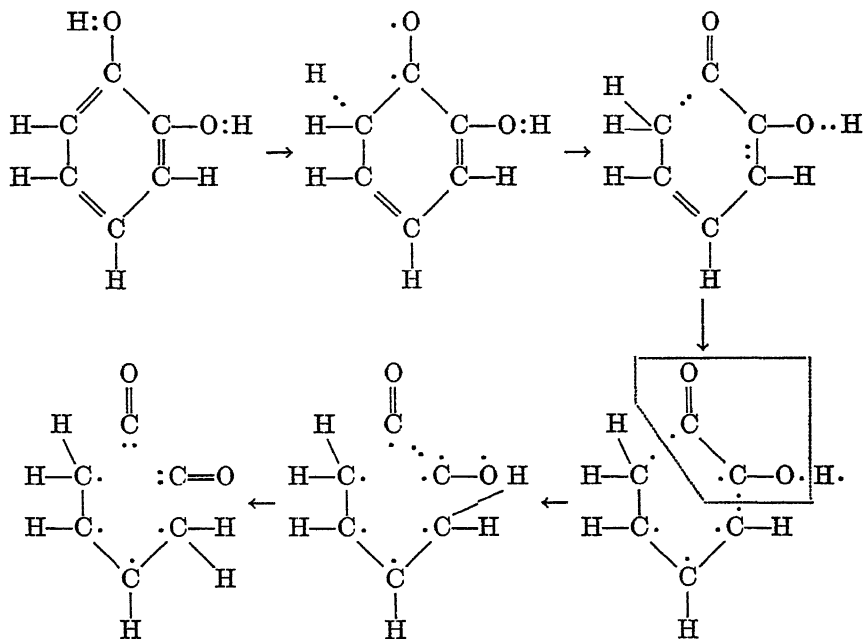According to the present authors, direct formation of butadiene seems indi-
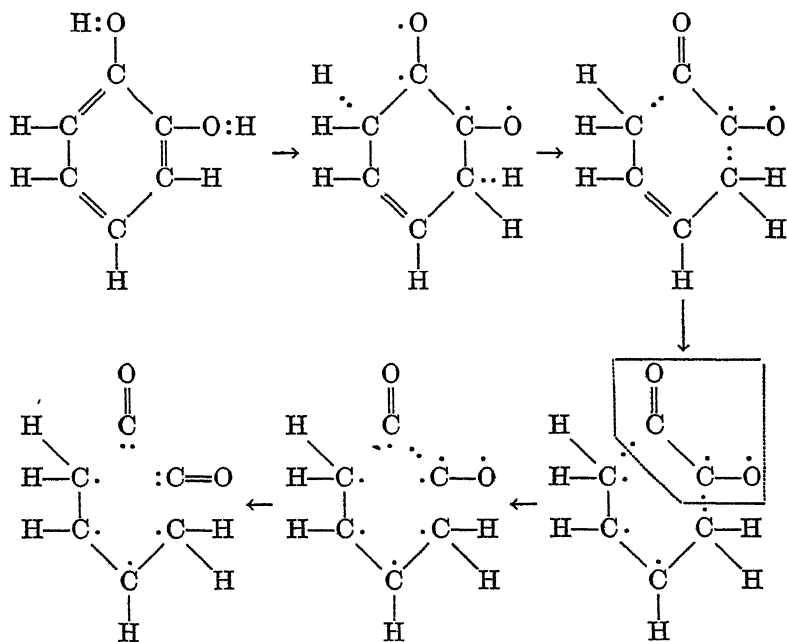cated on electronic grounds, as in the case of hydroxybenzene:
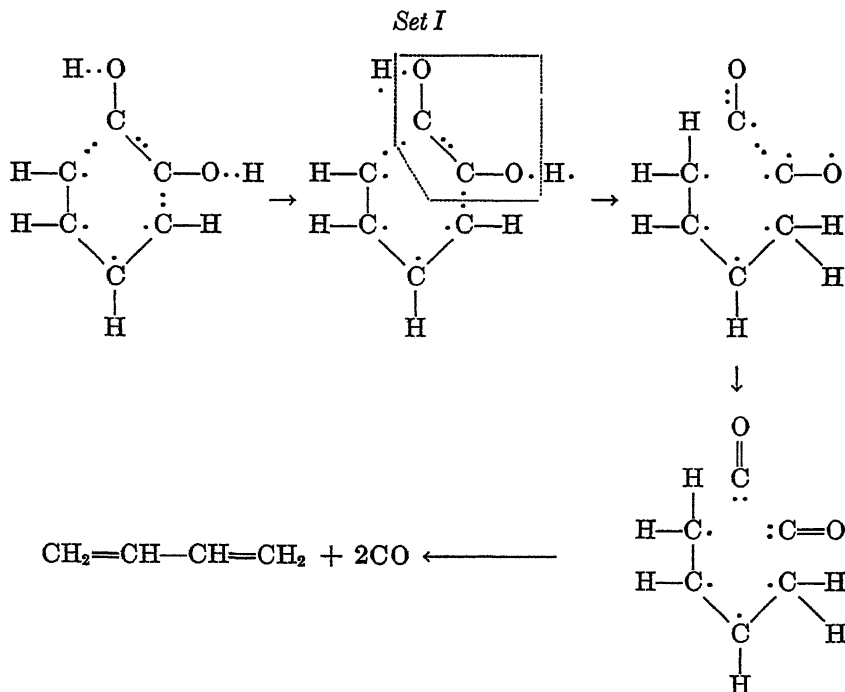
Set I

For the case of a prior tautomerization of 1,2-dihydroxybenzene into 2,4-
cyclohexadien-1-on-2-ol or to 4-cyclohexene-1,2-dione, a similar formulation
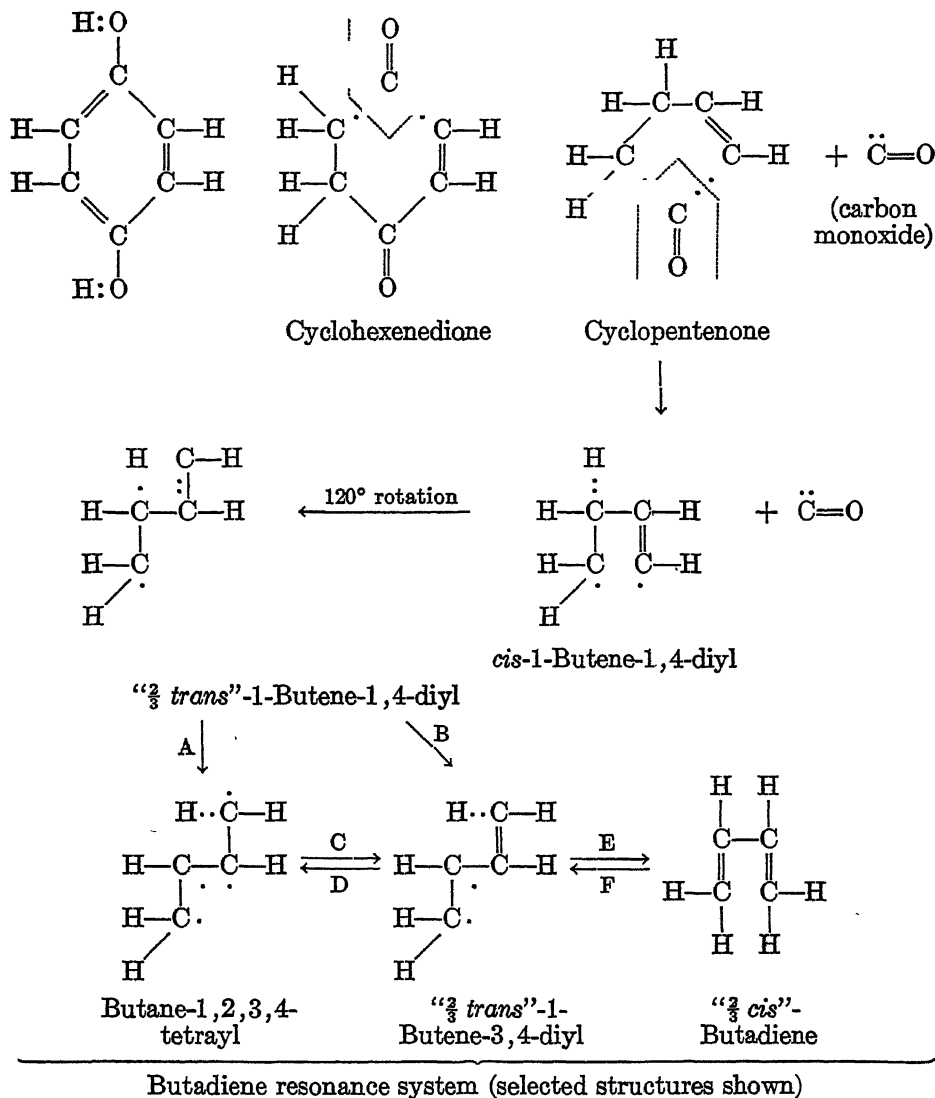can be given:

Set II

Set III

All three sets of transformations should be 17.4 kcal. endothermic per gram-nole of butadiene produced, assuming 39.4, 5.0, and 2 × 58 kcal. as the total nolal resonance energies of the dihydroxybenzene, butadiene, and carbon nonoxide, respectively.

Less butadiene is yielded by 1,3-dihydroxybenzene than by either 1,2- or ,4-dihydroxybenzene. Upon contact with glass rings at 650°C., 1,3-dihy-lroxybenzene forms hydrogen, carbon, carbon monoxide, carbon dioxide, nethane, ethene, butadiene, and aromatic condensation products (49). At .emperatures of 300–380°C., 1,3-dihydroxybenzene begins to lose carbon dioxide ind forms aromatic condensation products, some of which are soluble in alkali. Nevertheless, formation of the alkadiene was ascribed to hydrogenation of C_4H_4 is for the case of 1,2-dihydroxybenzene. The present authors cannot accept .his version of the mechanism, because no C_4H_4 is directly derivable from 1,3-lihydroxybenzene by formation of two molecules of carbon monoxide. Iso-nerization to 1,2-dihydroxybenzene is postulated as the probable initial reac-;ion leading to butadiene formation. In favor of this interpretation can be cited ;he low yield of alkadiene, which corresponds to the expected low extent of .somerization of meta into ortho derivatives. Again a higher yield should be)btained from 1,4- than from 1,3-dihydroxybenzene. This is found to be the ;ase.

Upon passage with some nitrogen over glass rings at 650°C., 1,4-dihydroxy-benzene produces large amounts of butadiene and carbon monoxide (49). The ɜquation given for the conversion was identical with that for 1,2-dihydroxyben-zene. Since formation of a C_4H_4 residue and *direct* removal of two molecules of carbon monoxide per ring are incompatible, an alternative isomerization to 1,2-dihydroxybenzene is indicated. In lieu of isomerization, tautomerization to 2-cyclohexene-1,4-dione could be postulated. This dione, upon loss of one carbonyl group, might form 2-cyclopenten-1-one, which would require further decarbonylation to give a C_4H_6 fragment (1-butene-1,4-diyl) capable of iso-merization to butadiene.

Cyclohexenedione   Cyclopentenone   + $\ddot{C}$=O

(carbon monoxide)

cis-1-Butene-1,4-diyl

"$\frac{2}{3}$ *trans*"-1-Butene-1,4-diyl

120° rotation   + $\ddot{C}$=O

Butane-1,2,3,4-tetrayl   "$\frac{2}{3}$ *trans*"-1-Butene-3,4-diyl   "$\frac{2}{3}$ *cis*"-Butadiene

Butadiene resonance system (selected structures shown)

The depicted 1-butene-1,4-diyl would obviously be of *cis* structure at the moment of its formation. Molecular models give further information. A 120° rotation of the ethenediyl group about the ethanediyl group would bring a 3-position hydrogen atom in proximity to the carbon atom in the 1-position, permitting changes A and B to occur. Change A represents a hydrogen migration akin to that of a tautomerization, whereas change B takes advantage of the availability of the lone electron in the 1-position. The similar electronic and spatial configurations of butanetetrayl and 1-butene-3,4-diyl call for arrows C and D. These poly-yls enter into resonance among the other valence-bond structures of butadiene. Change E represents a particularly easy way of ob-

TABLE 9

Conversion of cyclanols and of hydroxybenzenes into butadiene

PROCESS AND STARTING DERIVATIVE	APPARATUS AND CATALYST	TEMPERATURE	PRESSURE	REMARKS (B IS 1,3-BUTADIENE)	REFERENCES
		°C.	atm.		
"Dehydration" of cyclopropylcarbinol H_2C——$CHCH_2OH \rightarrow C_4H_6 + H_2O$ with CH_2	Catalyst: Al_2O_3	300–400	?	Yield of B was 5.6% by weight on feed	(19)
"Dehydration" of cyclobutanol H_2C—$CHOH$ / H_2C—CH_2 $\rightarrow C_4H_6 + H_2O$	Catalyst: Al_2O_3	?	?	Yield of B = ?	(126)
	Catalyst: Al_2O_3	300–350		Yield of B was 75% by weight	(131)
	Catalyst: Al_2O_3	360–390		Yield of B was 5.6% by weight on feed	(19)
Dehydration and partition of 1-methyl-3-cyclopentanol H CH_3 C H_2C CH_2—$CHOH$ H_2C—$CHOH$ $\rightarrow C_4H_6 + H_2O + C_2H_4$ (Probable reaction is given)	Copper tube containing silver gauze inside	Dark red heat	1	Yield of B = ?	(29)
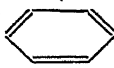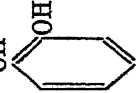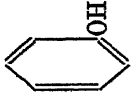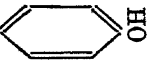
Reaction	Apparatus	Temperature	Ratio	Yield	Ref.
Dehydration and partition of dimethylcyclo-pentanols $C_5H_7(CH_3)_2(OH) \rightarrow C_4H_6 + H_2O + C_2H_6$ (Possible reaction is given)	Not described (probably a copper tube containing silver gauze)	Dark red heat?	1?	Yield of B = ?	(29)
Dehydration and partition of cyclohexanol OH $\rightarrow C_4H_6 + H_2O + C_2H_4$	Iron tube which can be filled with native Al_2O_3	600	1	Yield of B was "good"	(54)
	Iron pipe	600	1	Yield of B = ?	(27)
	Quartz tube	Slight red heat	1	Yield of B was 22–28% by weight on feed; tubes of quartz, platinum, or silver are better than those of iron or porcelain	(26)
Catalytic cracking of hydroxybenzene (i.e., phenol) OH $\rightarrow C_4H_6 + CO + C$ (Probable reaction is given)	Catalyst: pumice	650–750	1?	Yield of B = ?	(49)

TABLE 9—*Continu*

PROCESS AND STARTING DERIVATIVE	APPARATUS AND CATALYST	TEMPERATURE °C.	PRESSURE atm.	REMARKS (B is 1,3-butadiene)	REFERENCES
Catalytic cracking of 1,2-dihydroxybenzene (i.e., pyrocatechol) $\to C_4H_6 + 2CO$	Quartz tube containing glass rings	650	1?	Yield of B was 21.1% by weight on feed	(49)
Catalytic cracking of 1,3-dihydroxybenzene (i.e., resorcinol) $\to C_4H_6 + 2CO$	Quartz tube containing glass rings	650	1?	Yield of B = ?	(49)
Catalytic cracking of 1,4-dihydroxybenzene (i.e., hydroquinone) $\to C_4H_6 + 2CO$	Quartz tube containing glass rings	650	1?	Yield of B = ?	(49)

taining strictly covalent butadiene, even if momentarily and, according to molecular models, with only two-thirds orientation toward perfect *cis* configuration.

Table 9 gives data on the conversion of cyclanols and hydroxybenzenes into butadiene.

III. OXIDE DERIVATIVES OF HYDROCARBONS

A. ALIPHATIC OXIDES

1. *Dialkyl ethers*

Diethyl ether undergoes a main dehydration to ethene and a lesser dehydration-dehydrogenation to butadiene at 600°C. over initially clean aluminum (34, 35, 95):

$$C_2H_5OC_2H_5 \rightarrow 2C_2H_4 + H_2O$$

$$C_2H_5OC_2H_5 \rightarrow CH_2\!\!=\!\!CH\!\!-\!\!CH\!\!=\!\!CH_2 + H_2 + H_2O$$
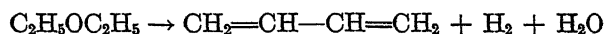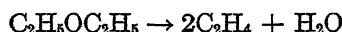
The metal becomes gradually coated with carbon and probably undergoes a certain amount of oxidation through contact with water vapor:

$$3C_2H_5OC_2H_5 \rightarrow 3CH_2\!\!=\!\!CH\!\!-\!\!CH\!\!=\!\!CH_2 + 3H_2O + 3H_2$$

$$3H_2O + 2Al \rightarrow Al_2O_3 + 3H_2$$

$$\overline{}$$

$$3C_2H_5OC_2H_5 + 2Al \rightarrow 3CH_2\!\!=\!\!CH\!\!-\!\!CH\!\!=\!\!CH_2 + Al_2O_3 + 6H_2$$
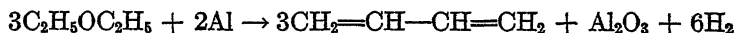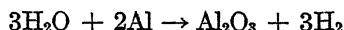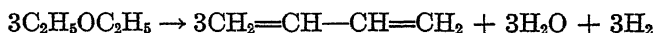
Filippov assumed that ethanal, which is found among the products, participates in butadiene formation. Ostromyslenskiĭ considered the conversion to involve probably dehydration to 2-butene, dehydrogenation to cyclobutene, and isomerization of the latter (136):
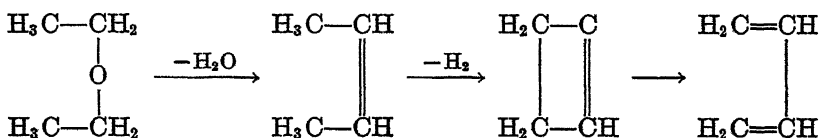
A possible dehydrogenation to 1,4-epoxybutane prior to dehydration was not overlooked (137, 142):
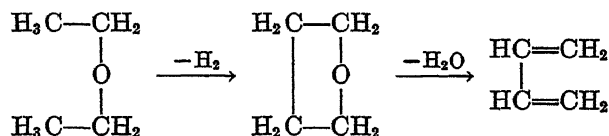
There are several reasons why butadiene should be formed from diethyl ether over aluminum at 300–600°C. First, ethanol and ethene, which are respectively expected and actual products, are each directly convertible into butadiene under similar conditions (21, 23, 72). Ethanal, another product, upon dimerization to 3-hydroxybutanal, with or without dehydration to 2-butenal, would be a further source of alkadiene. However, ethanol probably must be simultaneously

present to effect a reduction to 1,3-butanediol and 2-buten-1-ol, respectively (24).

In formulating a probable course for the conversion of diethyl ether into butadiene, one must take cognizance of the probable preliminary scission into ethoxyl and *ethyl radicals*. The latter, upon loss of two hydrogen atoms apiece, would form vinyl radicals. These upon association form butadiene.

Monosubstituted diethyl ethers undergo vapor-phase catalytic dehydration, forming butadiene as a common product (126). These ethers have the general formula $C_2H_5OC_2H_4R$, in which R may be a halo, hydroxyl, alkoxy, or acyloxy group. The following radicals were utilized: α-chloro, β-chloro, α-hydroxy, α-ethoxy, and α-acetoxy. Five corresponding equations are:

$$C_2H_5OCHClCH_3 \xrightarrow{Al_2O_3 + BaO} CH_2{=}CH{-}CH{=}CH_2 + H_2O + HCl$$

$$C_2H_5OCH_2CH_2Cl \longrightarrow CH_2{=}CH{-}CH{=}CH_2 + H_2O + HCl$$

$$C_2H_5OCH(OH)CH_3 \longrightarrow CH_2{=}CH{-}CH{=}CH_2 + 2H_2O$$

$$C_2H_5OCH(OC_2H_5)CH_3 \xrightarrow{Al_2O_3} CH_2{=}CH{-}CH{=}CH_2 + H_2O + C_2H_5OH$$

$$C_2H_5OCH(OCOCH_3)CH_3 \rightarrow CH_2{=}CH{-}CH{=}CH_2 + H_2O + CH_3COOH$$
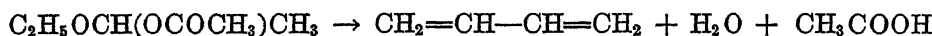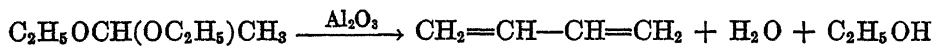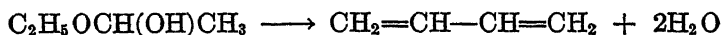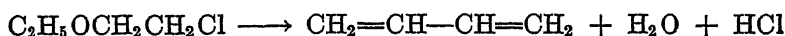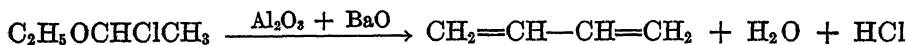
Catalytic conversion of ethyl β-hydroxyethyl ether substantiates the foregoing equations (8):

$$C_2H_5OCH_2CH_2OH \xrightarrow{Al_2O_3 \text{ or } TiO_2} CH_2{=}CH{-}CH{=}CH_2 + 2H_2O$$
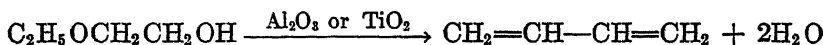
Ostromyslenskiĭ mentioned the mechanism of conversion of substituted diethyl ethers and the equilibrium existing between α-hydroxyethyl ether, ethanol, and ethanal (129). This ether, at 360–440°C., evidently undergoes a complete and facile dissociation into ethanol and ethanal, followed by interaction (condensation) of these components. Although Ostromyslenskiĭ had discovered that ethyl vinyl ether (126) and its isomer, 1,4-epoxybutane (125, 126), both yield butadiene under the same conditions, an interrelationship between these compounds, such as the following equation submitted by the authors, was not considered (X is a halo, hydroxyl, alkoxy, or acyloxy group):

$$C_2H_5OCHXCH_3 \xrightarrow{-HX} C_2H_5OCH{=}CH_2 \longrightarrow$$
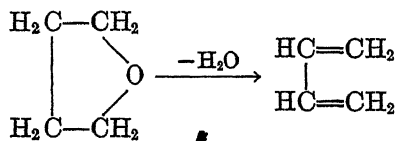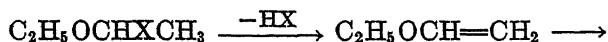
Methyl α-methoxyethyl ether appears to be but slightly convertible into butadiene over alumina-containing catalysts (4, 79). The present authors offer the following mechanisms for the converted portion: (*a*) an initial demethanolation to methyl vinyl ether, supplemented by scissions affording vinyl radicals which associate; (*b–c*) an initial removal of dimethyl ether with formation of ethanal,

which is convertible into butadiene by way of aldolization and either reduction to 1,3-butanediol or dehydration followed by reduction to 2-buten-1-ol; and (d) a high-energy barrier "bidehydration" into two methylene radicals plus ethane-1,1,2,2-tetrayl, followed by appropriate combination to butane-1,2,3,4-tetrayl.

When autoclaved at 140–200°C. in the presence of dilute sulfuric or other acids, γ,γ'-dihydroxydibutyl ether dehydrates to butadiene (50):

$$CH_3CHOHCH_2CH_2—O—CH_2CH_2CHOHCH_3 \rightarrow$$

$$2CH_2\!=\!CH—CH\!=\!CH_2 + 3H_2O$$
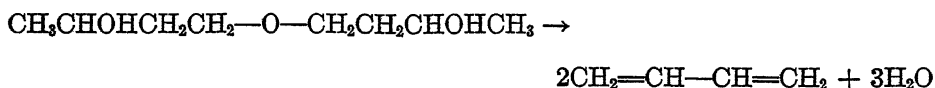
It is desirable to remove the alkadiene from the reaction zone as fast as it is formed. Formation of 2 gram-moles of butadiene from γ,γ'-dihydroxydibutyl ether requires 12.8 kcal., independently of the chosen reaction course. Assuming that C—C scissions requiring 58.6 kcal. need not be considered, the following five interpretations of the reaction can be given:

1. Preliminary formation of γ-hydroxybutyl 2-buten-1-yl ether, followed by further change into one or more related compounds:
   (a) di(2-buten-1-yl) ether (dicrotyl ether)
   (b) 1,3-butadiene plus 1,3-butanediol
   (c) 1-buten-3-ol plus 2-buten-1-ol
2. Initial decomposition to 1,3-butanediol plus 1-buten-3-ol
3. Cyclization to 2,8-dimethyl-1,5-dioxocane, i.e., 2,8-dimethyl-1,5-dioxacyclooctane, followed by decyclization to:
   (a) 1-butanol-3-yl 3-buten-2-yl ether
   (b) γ-hydroxybutyl 2-buten-1-yl ether
   (c) γ-hydroxybutyl 3-buten-1-yl ether
   (d) di(2-buten-1-yl) ether
   (e) di(3-buten-1-yl) ether
   (f) di(3-buten-2-yl) ether
4. Mono- or di-esterification, with deësterification to γ-hydroxybutyl 2-buten-1-yl ether or di(2-buten-1-yl) ether
5. Dissociation to 3-butanol-1-yl and 3-butanol-1-oxyl, followed respectively by disproportionations to:
   (a) 2-butanol plus 1-buten-3-ol
   (b) 1,3-butanediol plus 3-hydroxybutanal

A final choice of mechanism for the dehydration of γ,γ'-dihydroxydibutyl ether cannot be made at this time because of lack of experimental data. Conditions favorable to each of the five interpretations given could be devised.

Over barium chloride at 350°C. or over alumina at 450–500°C., under decreased pressure, γ-chlorobutyl γ'-hydroxybutyl ether undergoes a combined dehydrodechlorination and bidehydration (31):

$$CH_3CHClCH_2CH_2—O—CH_2CH_2CHOHCH_3 \rightarrow$$

$$2CH_2\!=\!CH—CH\!=\!CH_2 + HCl + 2H_2O$$
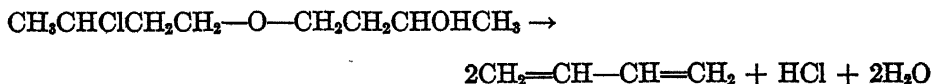
From a mechanism standpoint, the conversion is more complicated in nature than that of γ,γ'-dihydroxydibutyl ether. The location of primary scission probably depends upon relative strengths of bonds other than C—C, the availability or potential of the disrupting energy, and the particular type of catalyst present. It seems probable that the rôles of barium chloride and alumina are, respectively, those of dehydrodechlorination and dehydration catalysts. Hence an active mixture of catalysts to effect both types of catalysis seems desirable.

2. Alkyl alkenyl ethers

Ethyl vinyl ether undergoes a "catalytic" dehydration to butadiene, ostensibly according to the over-all equation (126):

$$CH_3CH_2\text{—}O\text{—}CH\text{=}CH_2 \rightarrow CH_2\text{=}CH\text{—}CH\text{=}CH_2 + H_2O$$

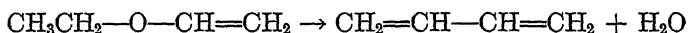From the reaction mechanism standpoint, it is probable that the radical less firmly attached to the oxygen atom will be mainly eliminated. According to molecular transposition studies (16, 17, 173, 177), the tendency of the vinyl group to split off is greater than that of the ethyl group. This fact introduces for consideration the following equations:

$$2CH_3\text{—}CH_2\text{—}O \cdot\cdot CH\text{=}CH_2 \rightarrow CH_2\text{=}CH:CH\text{=}CH_2 + 2CH_3\text{—}CH_2\text{—}\overset{\displaystyle\cdot}{O}$$

$$2CH_3\text{—}CH_2\text{—}\overset{\displaystyle\cdot}{O} \rightarrow 2CH_3CHO + H:H$$

$$CH_3CHO \rightarrow CH_4 + CO$$

$$2CH_3\text{—}CH_2\text{—}O \cdot\cdot CH\text{=}CH_2 \rightarrow CH_2\text{=}CH:CH\text{=}CH_2 + 2CH_3CHO \text{ (or}$$
$$2CH_4 + 2CO) + H:H$$
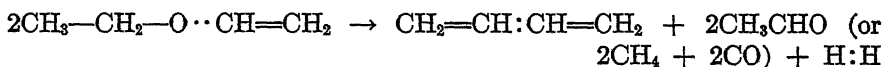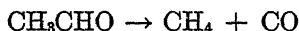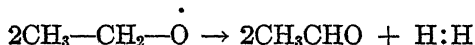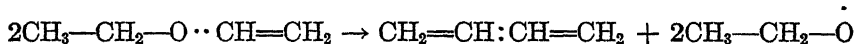
Alkyl α-vinyl-β-iodoethyl ethers readily form butadiene when acted upon by magnesium or zinc dust and ethanol (151). The alkyl group is suitably methyl, ethyl, n-propyl, or isobutyl:

$$ROCH(CH\text{=}CH_2)CH_2I + Mg(\text{or Zn}) \rightarrow$$
$$CH_2\text{=}CH\text{—}CH\text{=}CH_2 + ROMgI(\text{or ROZnI})$$
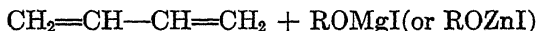
It will be observed that elimination of the alkoxyl groups is β to the vinyl group, hence rapid in rate, and that in the fragmentation the normally weak β C—C bond is stronger than the strained C—O bond. The C—I bond is probably the weakest linkage (45.5 kcal.) in the molecule, so that polar alkyl α-vinyl-β-iodomagnesium(or iodozinc)ethyl ethers may be taken as reaction intermediates. Elimination of alkoxymagnesium or alkoxyzinc iodide would occur with simultaneous establishment of resonance among butadiene structures, beginning with 1-butene-$\overset{+}{3},\overset{-}{4}$-diyl:

$$CH_2\text{=}CH\text{—}\overset{+}{CH}(\overset{\cdot\cdot}{O}R)\overset{\cdot\cdot}{CH_2}(\overset{+}{MgI}) \longrightarrow CH_2\text{=}CH\text{—}\overset{+}{CH}\text{—}\overset{\cdot\cdot}{CH_2} + RO:MgI$$
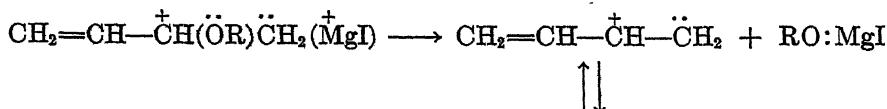
3. Dialkenyl ethers

Divinyl ether forms butadiene when reduced by iron, copper, lead, tin, bismuth, antimony, cadmium, zinc, or aluminum:

$$CH_2{=}CH\cdot\cdot O\cdot\cdot CH{=}CH_2 \;+\; metal \;\rightarrow\; CH_2{=}CH{:}CH{=}CH_2 \;+\; metal{::}O$$
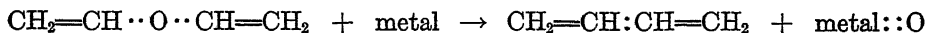
The process operates at 100–400°C. (102, 103, 104, 105). One would expect in this reaction a certain amount of dehydration traceable to the metal oxides produced. A dehydration to ethyne or dissociation to ethanal plus ethyne, which would require respectively 48.2 and 9.4 kcal. per gram-mole of divinyl ether, is avoided or minimized presumably by an excess of metal reactant.

Dehydration of di(2-but-en-1-yl) ether was announced by Ostromyslenskiĭ (126):

$$CH_3CH{=}CHCH_2{-}O{-}CH_2CH{=}CHCH_3 \;\rightarrow\; 2CH_2{=}CH{-}CH{=}CH_2 \;+\; H_2O$$

First, 1,4-dehydration would give presumably 2-buten-1-ol plus butadiene and, second, more butadiene by conversion of the butenol. Each step would be only 0.7 kcal. endothermic, making the over-all process theoretically 1.4 kcal. endothermic per two gram-moles of butadiene.

Table 10 gives data on the conversion of the various aliphatic ethers into butadiene.

B. CYCLIC OXIDES

1. Epoxybutanes

The catalytic dehydration of 1,4-epoxybutane was discovered by Ostromyslenskiĭ (126):

$$\begin{array}{ccc} H_2C{-}{-}{-}CH_2 & & HC{-}CH \\ | \qquad\quad | & \longrightarrow & \parallel \quad \parallel \quad + H_2O \\ H_2C \qquad CH_2 & & H_2C \quad CH_2 \\ \diagdown \;\; \diagup & & \\ O & & \end{array}$$
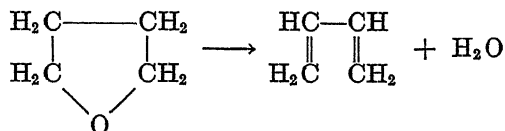
Catalysts for the conversion include the primary sodium, primary or secondary calcium, other alkaline earth, nickel, cobalt, silver, copper, mercury, and lead orthophosphates, phosphoric acid or boric acid on pumice or other carriers, heteropolyacids of tungsten or of molybdenum, oxides of tungsten or of molybdenum, silica gel, alumina, and chromia (61, 63, 64, 163). The acid phosphates may be used at 250–450°C. in the presence of steam. A later patent cites production of butadiene from 1,3- and 1,4-butanediols over acid phosphates in the presence of 1,4-epoxybutane as an organic diluent that is but slowly decomposed in the reaction (162). Since similar catalysts and temperatures are used in the production (60, 62, 69, 70, 160, 161, 164) of 1,4-epoxybutane from 1,4-butanediol, the possibility of formation of a weak bond between 1,4-epoxybutane and the catalysts is indicated; decomposition of the oxonium salts into butadiene would be the next step.

At 400–500°C. over pumice carrying orthophosphoric acid, 2,3-epoxybutane

TABLE 10

Conversion of ethers into butadiene

PROCESS AND ETHER USED	CATALYSTS OR SPECIAL REACTANTS	TEMPER-ATURE	PRESSURE	REMARKS (B IS 1,3-BUTADIENE)	REFERENCES
		°C.	atm.		
"Dehydration" and dehydrogenation of diethyl ether $3(C_2H_5)_2O + 2Al \rightarrow 3C_4H_6 + Al_2O_3 + 6H_2$	Aluminum metal was a reactant	600		Yield of B was small on fully decomposed ether	(34, 35)
	Aluminum metal was a reactant			Yield of B was 2% on ether	(98)
	A catalyst of undisclosed composition was used	450	0.974–0.987	Yields of B were 7% (average) and 10% (maximum) by weight on ether passed and 9–10% (average) by weight on fully decomposed ether	(95)
"Dehydration" and dehydrodechlorination of ethyl α-chloroethyl ether (mono-α-chlorodiethyl ether) $C_2H_5OCHClCH_3 \rightarrow C_4H_6 + H_2O + HCl$	Catalyst: $Al_2O_3 + BaO$	350		Yield of B was 20%	(142)
	Catalyst: Al_2O_3			See patent for possible details	(126, 139)
"Dehydration" and dehydrodechlorination of ethyl β-chloroethyl ether (mono-β-chlorodiethyl ether) $C_2H_5OCH_2CH_2Cl \rightarrow C_4H_6 + H_2O + HCl$	A catalyst was used			See patent for possible details	(126, 139)
"Dehydration" of ethyl α-hydroxyethyl ether $C_2H_5OCHOHCH_3 \rightarrow C_4H_6 + 2H_2O$				See patent for possible details	(126, 139)
"Dehydration" of ethyl β-hydroxyethyl ether $C_2H_5OCH_2CH_2OH \rightarrow C_4H_6 + 2H_2O$	Catalyst: Al_2O_3 or ThO_2	400–450			(8)

Reaction	Conditions	Temp.		Notes	Ref.
	Catalyst: Al_2O_3	350		Yield of B = ?	(4)
Decomposition of methyl α-methoxy-ethyl ether (1,1-dimethoxyethane) $CH_3OCH(OCH_3)CH_3 \rightarrow C_4H_6 + 2H_2O$	Catalysts were (1) Al_2O_3 1, ThO_2 0.045, activated clay 5.225 parts; (2) Al_2O_3 1, $NiCl_2$ 0.01, activated clay 5.05 parts; (3) Al_2O_3 1, ThO_2 0.045, activated clay 5.225 parts	450		Yields of B were 0.051, 0.064, and 0.060% by weight on feed for catalysts 1, 2, and 3, respectively	(79)
Decomposition of ethyl α-ethoxyethyl ether (acetal or 1,1-diethoxyethane) $C_2H_5OCH(OC_2H_5)CH_3 \rightarrow C_4H_6 + H_2O + C_2H_5OH$	Catalyst: Al_2O_3	300–380		Yield of B was 16%	(142)
"Dehydration" and deësterification of ethyl α-acetoxyethyl ether (mono-α-acetoxydiethyl ether) $C_2H_5OCH(OCOCH_3)CH_3 \rightarrow C_4H_6 + H_2O + CH_3COOH$				See patent for possible details	(126, 138)
Dehydration of γ,γ'-dihydroxydibutyl ether $(CH_3CHOHCH_2CH_2)_2O \rightarrow 2C_4H_6 + 3H_2O$	Catalyst was H_2SO_4 (1%) in water; an autoclave was used; acid sulfates, sulfonic acids, phosphoric acid, perchloric acid, or mixtures of these compounds may be used as catalysts	200	>15	Yield of B = ?	(50)
Dehydration and dehydrodechlorination of γ-chlorobutyl γ'-hydroxy-butyl ether $CH_2ClCHClCH_2CH_2OCH_2CH_2CHOHCH_3 \rightarrow 2C_4H_6 + HCl + 2H_2O$	Catalyst: $BaCl_2$	350	0.0395– 0.0526	Yield of B was 18% by weight on feed	(31)
	Catalyst: Al_2O_3	450–500	0.0658	Yield of B was 24% by weight on feed	(31)
"Dehydration" of ethyl vinyl ether $C_2H_5OCH{=}CH_2 \rightarrow C_4H_6 + H_2O$				See patent for possible details	(126, 138)

TABLE 10—Continued

PROCESS AND ETHER USED	CATALYSTS OR SPECIAL REACTANT	TEMPER- ATURE °C.	PRESSURE atm.	REMARKS (B IS 1,3-BUTADIENE)	REFERENCES
Deiododemethoxylation of methyl α-vinyl-β-iodoethyl ether $CH_3OCH(CH{=}CH_2)CH_2I + Mg$ (or Zn) $\rightarrow$ $C_4H_6 + CH_3OMgI$ (or CH_3OZnI)			1	Yield of B = ?; ethanol was part of the feed	(151)
Deiododeëthoxylation of ethyl α-vinyl-β-iodoethyl ether $C_2H_5OCH(CH{=}CH_2)CH_2I + Mg$ (or Zn) $\rightarrow C_4H_6 + C_2H_5OMgI$ (or C_2H_5OZnI)			1	Yield of B = ?; ethanol was part of the feed	(151)
Deiododepropoxylation of propyl α-vinyl-β-iodoethyl ether $C_3H_7OCH(CH{=}CH_2)CH_2I + Mg$ (or Zn) $\rightarrow C_4H_6 + C_3H_7OMgI$ (or C_3H_7OZnI)			1	Yield of B = ?; ethanol was part of the feed	(151)
Deiododeisobutoxylation of isobutyl α-vinyl-β-iodoethyl ether $C_4H_9OCH(CH{=}CH_2)CH_2I + Mg$ (or Zn) $\rightarrow C_4H_6 + C_4H_9OMgI$ (or C_4H_9OZnI)			1	Yield of B = ?; ethanol was part of the feed	(151)
Reduction of divinyl ether $(CH_2{=}CH)_2O + metal \rightarrow C_4H_6 + metal$ oxide	Fe, Cu, Pb, Sn, Bi, Sb, Cd, Zn, and Al are reactants	140–400	?	Yields of B = ?	(102, 103)
Reduction of divinyl ether by zinc $(CH_2{=}CH)_2O + Zn \rightarrow C_4H_6 + ZnO$	Zn is a reactant	?	?	Yield of B = ?	(104)
Reduction of divinyl ether $(CH_2{=}CH)_2O + metal \rightarrow C_4H_6 + metal$ oxide	Fe, Cu, Pb, Sn, Bi, Sb, Cd, and Zn are reactants	100–400	?	Yields of B = ?	(105)
"Dehydration?" of di(2-buten-1-yl) ether $(CH_3CH{=}CHCH_2)_2O \rightarrow 2C_4H_6 + H_2O$		?	?	Yield of B = ?	(126, 129)

undergoes dehydration to butadiene (110). Owing to the high temperature range, some question exists concerning the type of dehydration—thermal or catalytic—that is operative.

2. Methyldioxane

When 4-methyl-*m*-dioxane, which can be called 1,3-butanediol formal, is conducted over a phosphoric acid on graphite catalyst at 270°C. in the presence of steam, butadiene, formaldehyde, water, and propene are formed (36):

$$\longrightarrow CH_2{=}CH{-}CH{=}CH_2 + HCHO + H_2O$$
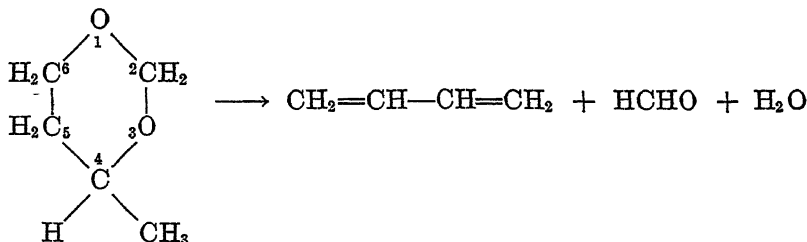
The conversion of 4-methyl-*m*-dioxane can be looked upon as a reversion into 1,3-butanediol and formaldehyde hydrate, followed by dehydration to butadiene:
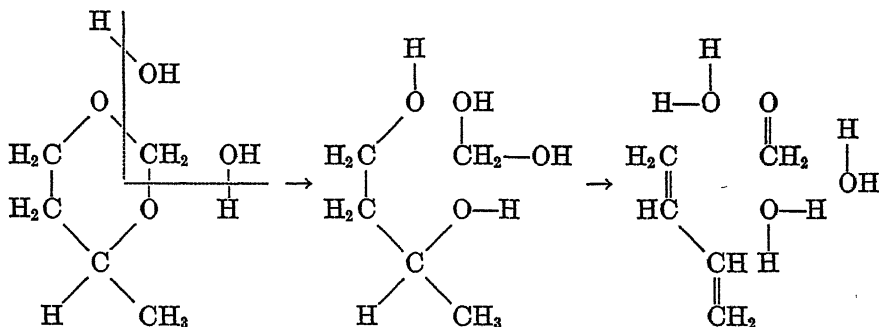
Table 11 contains data on the conversion of cyclic oxides into butadiene.

IV. ALDEHYDES

A. ALKANALS

Considerable theoretical interest lies in an electrolytic reduction and condensation of ethanal, patented twenty-five years ago (145):

$$2CH_3CHO + 2H \rightarrow CH_2{=}CH{-}CH{=}CH_2 + 2H_2O$$

The by-products include 1,3-butanediol and butenols, the formation of which was ascribed to hydrogenation of 3-hydroxybutanal and of its dehydration product, 2-butenal, respectively. Abundant evolution of hydrogen at the cathode leads to formation of 1-butanol. From this point of view, butadiene production is dependent on aldolization, hydrogenation, and dehydration. The order

TABLE 11

Catalysis of cyclic oxides

PROCESS AND CYCLIC OXIDE	CATALYST	TEMPERATURE °C.	PRESSURE atm.	REMARKS (B IS 1,3-BUTADIENE)	REFERENCES
Dehydration of 1,4-epoxybutane (tetrahydrofuran) $H_2C\!-\!CH_2$, H_2C CH_2 with O, $\rightarrow C_4H_6 + H_2O$	. . . . A catalyst was used	. . . . Heated	. . . .	. . . . See patent for possible details	(125)
	Catalysts were: (A) mercurous phosphate on pumice; (B) calcium phosphate; (C) W_2O_5 + bleaching earth; (D) NaH_2PO_4 + H_3PO_4 + graphite + nickel acetate	280–290 (case A) 360 (case B) 330–390 (case C) 260–310 (case D)	1 or less (cases A, B, D) Approx. 1 (case C)	Yields of B were 71, (?), less than 49.4, less than 48.7% by weight on feed in cases A, B, C, and D, respectively	(126, 138) (163)
Dehydration of 2,3-epoxybutane $CH_3CH\!-\!CHCH_3 \rightarrow C_4H_6 + H_2O$ with O	H_3PO_4 on pumice	400–500	In vacuo if desired	Yield of B = ?	(110)
Decomposition of 4-methyl-m-dioxane in presence of steam $\rightarrow C_4H_6 + H_2O + HCHO$	H_3PO_4 on graphite (prepared at 160°C. from sodium phosphate solution, primary n-butylamine phosphate, and graphite)	270	1?	Yield of B was 52% by weight on absolute methyldioxane feed	(36)

of the last two reactions is questionable. An alternative mechanism that warrants attention is a simple type of condensation with a bidehydration. 2,3-Butanediol and 3-butanol-2-oxyl would then be the intermediates:

$$CH_3\text{—}\overset{\cdot}{HC}\cdot \;+\; \overset{\cdot}{H} \longrightarrow CH_3\text{—}\overset{\cdot}{HC}\cdot \longrightarrow \tfrac{1}{2}CH_3\text{—}HC\!:\!CH\text{—}CH_3$$

with the oxygens: $\overset{\cdot}{O}\cdot$; $O\!:\!H$; $HO \quad OH$

(2H₂O loss) — $(2H_2O\;loss)$ ↓

$$CH_3\text{—}CH\text{—}CH\!=\!CH_2 \quad \xrightarrow[\;(1H_2O\;loss)\;]{\overset{\cdot}{H}\;presence\;} \quad CH_2\!=\!CH\text{—}CH\!=\!CH_2$$

with $\cdot\overset{\cdot}{O}$

$(1H_2O\;loss)$ $(2H_2O\;loss)$

$$CH_3\text{—}CH\cdot \;+\; \cdot CH\text{—}CH_3 \rightarrow CH_3\text{—}CH\!:\!CH\text{—}CH_3 \xrightarrow{\;\overset{\cdot}{H}\;} CH_3\text{—}CH\text{—}CH\text{—}CH$$

with $\overset{\cdot}{O}\cdot \quad OH$; $\cdot O \quad OH$; $H\!:\!O \quad OH$

Since the electrolyte contained over 20 per cent of sulfuric acid and was maintained at temperatures above 30–35°C., a further pinacol type of rearrangement to 2-butanone seems possible. It would decrease the butadiene yield. Isolation of 2-butanol, 2-butanone, or 2,3-butanediol would fortify the foregoing mechanism.

Butanal is readily converted into butadiene by passage over aluminum silicate at 550°C. and an absolute pressure of 1 mm. of mercury (85, 149):

$$CH_3CH_2CH_2CHO \rightarrow CH_2\!=\!CH\text{—}CH\!=\!CH_2 + H_2O$$

The catalysis is not that of a simple dehydration. 1-Buten-1-ol, which corresponds to a probably tautomeric form of butanal at high temperatures, and cyclobutanol are hypothetical intermediates for a conversion through cyclobutene. An isomerization of 1-buten-1-ol into 2-buten-1-ol is another possibility; it would permit 1,4-dehydration and avoid cyclization.

When 2-methylpropanal is passed over pumice at 580–590°C. under atmospheric pressure, it yields a trace of butadiene (118). While the desired reaction may be a dehydration with intervening isomerization:

$$CH_3CHCHO \rightarrow \left[CH_3CH\text{—}CHOH;\; CH_2\!=\!CHCHCH_3;\; CH_2CH\!=\!CHCH_2 \right]$$

with CH_3 → CH_2 , OH , OH , H

↓

$$CH_2\!=\!CH\text{—}CH\!=\!CH_2 + H_2O$$

the other products, i.e., hydrogen, water, carbon monoxide, methane, ethane, ethene, propene, ethanal, and probably 2-butenal, are indicative of a variety of competitive reactions. Demethylation to propanal-α-yl and ethanal-α,α-diyl is expected, accounting for the presence of C₁, C₂, and C₃ products. The car-

bonyl group is removed by direct elimination and as water (traceable to tauto-
merization of HC—C=O into C=C—OH or to carbonyl hydrogenations,
$\overset{..}{C}$—$\overset{.}{O}$ + $\overset{.}{H}$ → $\overset{.}{C}$—O:H; $\overset{..}{C}$—$\overset{.}{O}$ + 2$\overset{.}{H}$ → H:C—O:H). Formation of ethane
and of ethene indicates a possible butadiene production through dehydrogena-
tion into vinyl radicals and their association. Demethanation of 2-methyl-
propanal into propenal, followed by decarbonylation or deformylation, is another
mechanism that would furnish vinyl radicals.

Ethanol converts 3-hydroxybutanal into butadiene when passed over lumps of
aluminum hydroxide at 300°C. (111). Steam is used to minimize resinification
of the hydroxybutanal and to keep the catalyst clean.

B. ALKENALS

2-Butenal, i.e., crotonaldehyde, is convertible into butadiene by reaction
with ethanol (111), ammonia (56), or aniline (55). The conditions for a reaction
with ethanol are exposure to temperatures of 250–460°C. in the presence of a
"dehydration" catalyst, such as lumps of precipitated aluminum hydroxide (111).

Ammonia reacts with 2-butenal at 390°C. in the presence of alumina, pro-
ducing ethene, butadiene, benzene, toluene, o-xylene, p-xylene, ethylbenzene,
styrene, naphthalene, acetonitrile, benzonitrile, o-tolunitrile, p-tolunitrile, pyr-
role, and 3-ethyl-4-methylpyridine, i.e., β-collidine (56). Huntenburg pointed
out that alumina could act as a catalyst, effecting removal of both ammonia
(57) and water from 2-butenalammonia:

$$CH_3CH=CHCH(OH)NH_2 \rightarrow [C_4H_4] + H_2O + NH_3$$
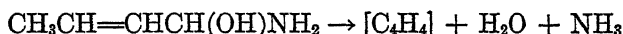
and that 2-butenal upon loss of water should form a C_4H_4 member, perhaps
butenyne or cyclobutadiene:

$$CH_3CH=CHCHO \qquad HC\equiv C—CH=CH_2 \quad \text{or} \quad \begin{array}{c} HC=CH \\ | \\ HC=CH \end{array} \quad + \quad H_2O$$
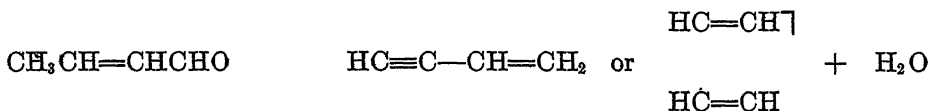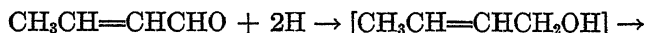
Hydrogenation of cyclobutadiene, which is generally acknowledged to be an
unstable molecule, because of ring strain (101, 148, 179, 180), was taken as
probably responsible for butadiene production:

$$\begin{array}{c} HC=CH \\ | \quad | \\ HC=CH \end{array} + 2\overset{.}{H} \longrightarrow CH_2=CH—CH=CH_2$$
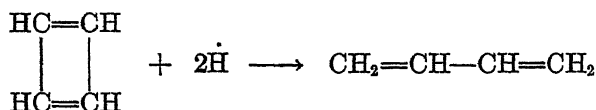
Dehydration of the aminohydroxymethyl group of 2-butenalammonia and
ethanalammonia, $CH_3CH(OH)NH_2$, would produce aldimines, RCH=NH,
whose dehydrogenation to nitriles could furnish the requisite hydrogen atoms
for hydrogenation of C_4H_4 into C_4H_6. Aldimines were taken as the source of
both tolunitriles and acetonitrile. The present authors suggest that ammonia
may function also as a source of atomic hydrogen, reducing the 2-butenal car-

bonyl group to the primary alcohol group of 2-buten-1-ol, which would be directly convertible into butadiene.

Aniline reacts with 2-butenal at temperatures above 500°C. in the presence of oxides of aluminum, beryllium, iron, or thorium (55). The products include butadiene, N-phenylpyrrole, 4-methylquinoline, and smaller amounts of ethene, benzene, xylene, styrene, naphthalene, hydroxybenzene, o-methybenzaldehyde, quinoline, and 2-methylquinoline. By increasing the proportion of aniline or passing over the catalyst at the same time such hydrogen donors as methanol or tetrahydronaphthalene, the butadiene yield is increased. N-Phenylpyrrole production increases if the temperature is above 600°C. and a large amount of aniline is introduced. Consequently, it can be postulated that the N-phenyl-pyrrole, 4-methylquinoline, and butadiene formations are related, with the atomic hydrogen released in 2-butenal and aniline condensations being used to transform 2-butenal into 2-buten-1-ol:

$$CH_3CH{=}CHCHO \ + \ H_2NC_6H_5 \ \rightarrow \ [CH_3CH{=}CHCH{=}NC_6H_5] \ + \ H_2O$$

(loss of 2H)

$$CH_3CH{=}CHCHO + 2H \rightarrow [CH_3CH{=}CHCH_2OH] \rightarrow$$

$$CH_2{=}CH{-}CH{=}CH_2 + H_2O$$
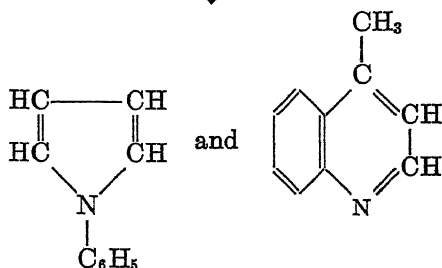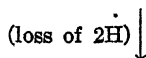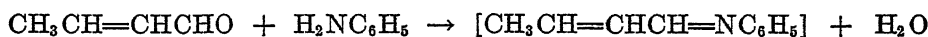
The over-all equation is identical for both the $C_{10}H_9N$ isomers:

$$2CH_3CH{=}CHCHO + C_6H_5NH_2 \rightarrow C_4H_6 + C_{10}H_9N + 2H_2O$$

Table 12 contains data on the conversion of aldehydes into butadiene.

V. CARBOXYLIC ACIDS AND THEIR ESTERS

A. ALKANOIC ACIDS

n-Butyric, isobutyric, and isovaleric acids form traces of butadiene upon passage over pumice at 600°C., according to Nef (122). A variety of reactions are operative in these pyrolyses, for the product in each case contains carbon monoxide, carbon dioxide, hydrogen, water, methane, ethane, ethene, propene, butadiene, and a keto compound (dimethyl ketone in the case of isobutyric acid). While butadiene formation could be attributed to an association of vinyl groups or to a polymerization of the ethene or propene with subsequent decomposition, there are other possibilities based on the chemistry of alkanoic acids.
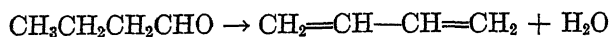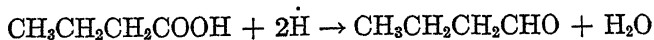
TABLE 12

Conversion of aldehydes into butadiene

PROCESS AND ALDEHYDE USED	CATALYST	TEMPERATURE °C.	PRESSURE atm.	REMARKS (B is 1,3-butadiene)	REFERENCES
Electrolytic reduction and condensation of ethanal (acetaldehyde) $2CH_3CHO + 2H \rightarrow C_4H_6 + 2H_2O$	Electrolyte had over 20% of H_2SO_4	>30–35		Yield of B = ?	(145)
"Dehydration" of butanal (butyraldehyde) $CH_3CH_2CH_2CHO \rightarrow C_4H_6 + H_2O$	Catalyst: aluminum silicate	550	0.00132	Yield of B was 52.5% by weight on feed, using one recycle	(85)
	Catalyst: aluminum silicate	Red heat		Yield of B = ?	(149)
"Dehydration" of 2-methylpropanal (isobutyraldehyde) $(CH_3)_2CHCHO \rightarrow C_4H_6 + H_2O$	Catalyst: pumice	580–590	1	Yield of B was 0.095% by weight on feed	(118)
Action of ethanol on 3-hydroxybutanal (aldol) $CH_3CHOHCH_2CHO + C_2H_5OH \rightarrow C_4H_6 + CH_3CHO + 2H_2O$ $CH_3CHOHCH_2CHO + 2C_2H_5OH \rightarrow 2C_4H_6 + 4H_2O$ (Probable reactions are given)	Catalyst: lumps of precipitated $Al(OH)_3$	300		Yield of B was 10.8% by weight on aldol feed	(111)
Action of ethanol on 2-butenal (crotonaldehyde) $CH_3CH=CHCHO + C_2H_5OH \rightarrow C_4H_6 + CH_3CHO + H_2O$ $CH_3CH=CHCHO + 2C_2H_5OH \rightarrow 2C_4H_6 + 3H_2O$ (Probable reactions are given)				Yield of B = ?	(111)

	Catalyst				
Action of ammonia on 2-butenal (crotonaldehyde)	Catalyst: Al_2O_3	390		Yield of B = ?	(56)
Action of aniline on 2-butenal (crotonaldehyde) $2CH_3CH=CHCHO + C_6H_5NH_2 \rightarrow C_4H_6 + C_{10}H_9N + 2H_2O$	Catalysts: Al_2O_3; BeO; iron oxide; ThO_2	Above 500	1 or less	Yield of B was 15% on product	(55)

The conversion of n-butyric acid into butadiene may be dependent on such reactions as:
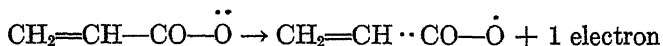
$$CH_3CH_2CH_2COOH + 2\dot{H} \rightarrow CH_3CH_2CH_2CHO + H_2O$$

$$CH_3CH_2CH_2CHO \rightarrow CH_2{=}CH{-}CH{=}CH_2 + H_2O$$

Isobutyric acid might be converted as follows:

$$(CH_3)_2CHCOOH + 4\dot{H} \rightarrow (CH_3)_2CHCH_2OH + H_2O$$

$$(CH_3)_2CHCH_2OH \rightarrow (CH_3)_2C{=}CH_2 + H_2O$$

$$(CH_3)_2C{=}CH_2 \rightarrow CH_3CH{=}CHCH_3 \ (\textit{trans})$$

$$CH_3CH{=}CHCH_3 \rightarrow CH_2{=}CH{-}CH{=}CH_2 + 2\dot{H}$$
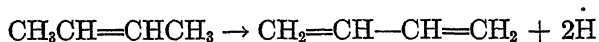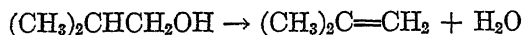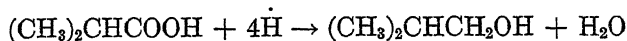
Isovaleric acid conversion into butadiene can be explained on the basis of decarboxylation, isomerization, and dehydrogenation.

B. ALKENOIC ACIDS

Ostromyslenskiĭ observed that electrolysis of acrylic acid gives small amounts of butadiene at the anode (136). The investigation was discontinued because of unavailability of a commercial supply and no explanation of the reaction course was given. A simple mechanism can be given by assuming that negative acrylate ions become neutralized at the anode, forming unstable acrylate free radicals:

$$CH_2{=}CH{-}CO{-}O{:}H \leftrightarrows CH_2{=}CH{-}CO{-}\overset{..}{O} + H$$

$$CH_2{=}CH{-}CO{-}\overset{..}{O} \rightarrow CH_2{=}CH\cdot\cdot CO{-}\overset{.}{O} + 1 \text{ electron}$$
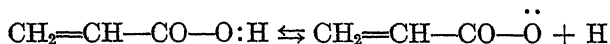
Decarboxylation of the latter would liberate vinyl radicals, some of which would associate to butadiene.

Oleic acid, which is cis-9-octadecenoic acid, yields 30 per cent of butadiene when its vapors are passed over a metal spiral heated to a bright red (40). The $trans$-form, or elaidic acid, also produces butadiene. These conversions are probably C_2 and C_4 scissions starting at the carboxyl or terminal methyl group, or in the β-position to the C=C group. Other points of weakness in the molecule are located two or four carbon atoms away from the positions of initial scission:

$$
\begin{array}{l}
H \\
\diagdown \\
H{-}C{-}\!|{-}CH_2{-}CH_2{-}\!|{-}CH_2{-}CH_2{-}\!|{-}CH_2{-}CH_2{-}\!|{-}CH_2{-}CH \\
\diagup \\
H
\end{array}
$$

$$
\begin{array}{l}
O \\
\diagdown\!\!\diagdown \\
C{-}\!|{-}CH_2{-}CH_2{-}\!|{-}CH_2{-}CH_2{-}\!|{-}CH_2{-}CH_2{-}\!|{-}CH_2{-}\overset{\parallel}{C}H \\
\diagup
\end{array}
$$
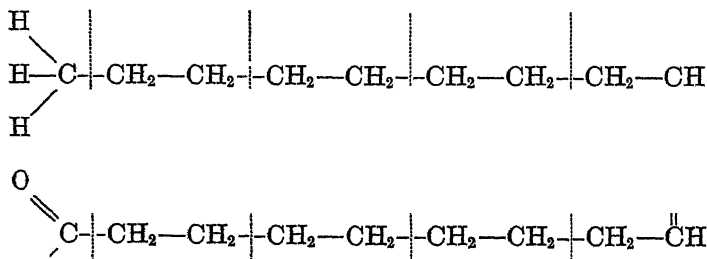
The C_2 and C_4 fragments, except 2-butene-1,4-diyl, require subsequent dehydrogenation to produce butadiene.

Calcium $\Delta^{\beta,\gamma}$-dihydromuconate forms butadiene, carbon monoxide, and 1-cyclopenten-3-one when dry-distilled (112). The theory advanced in explanation of the conversion was decarbonylation of the aforementioned cyclopentenone:
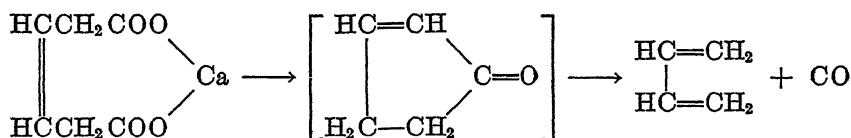
1-Cyclopenten-3-one may have considerable stability, whereas the expected dry-distillation ketone is 1-cyclopenten-4-one. The latter should undergo decarbonylation by β scissions alone:
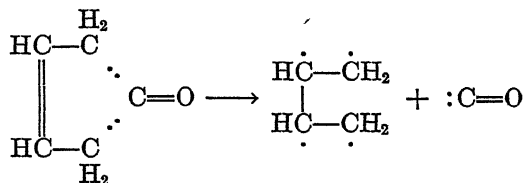
C. ALKADIENOIC ACID

2,4-Pentadienoic acid yields butadiene when distilled with quinoline (136). This conversion can be considered to involve dissociation of an unstable quinoline compound:
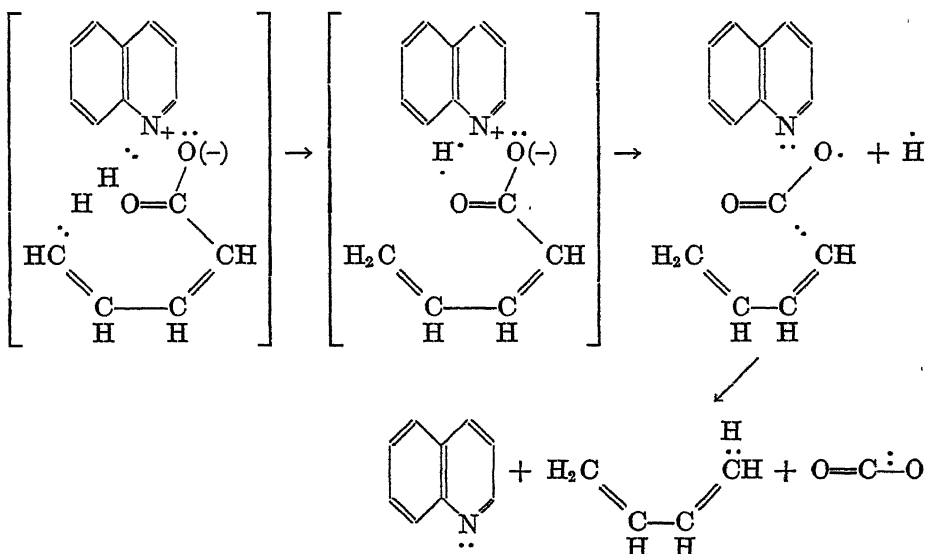
TABLE 13
Conversion of carboxylic acids into butadiene

PROCESS AND CARBOXYLIC ACID	APPARATUS AND CATALYSTS	TEMPERATURE	PRESSURE	REMARKS (B IS 1,3-BUTADIENE)	REFERENCES
		°C.	atm.		
Decomposition of *n*-butyric acid $2CH_3CH_2CH_2COOH \rightarrow C_4H_6 + C_3H_6 + CO_2 + 2H_2O$ (Probable reaction is given)	Catalyst: pumice	590–600	1	Yield of B was 0.22% by weight on feed	(122)
Decomposition of isobutyric acid $2(CH_3)_2CHCOOH \rightarrow C_4H_6 + C_2H_6 + CO_2 + 2H_2O$ (Probable reaction is given)	Catalyst: pumice	600–620	1	Yield of B was 0.029% by weight on feed	(122)
Decomposition of isovaleric acid $(CH_3)_2CHCH_2COOH \rightarrow C_4H_6 + CO_2 + 2H_2$	Catalyst: pumice	600	1	Yield of B was 0.082% by weight on feed	(122)
Electrolysis of acrylic acid $2CH_2{=}CHCOOH \rightarrow C_4H_6 + 2CO_2 + H_2$				Yield B of = ?; no details available	(136)
Thermal treatment of vapors of technical oleic acid (olein, stearin oil)	Iron vessel serving as vaporizer; an attached vertical column containing a metal spiral heated by electricity serving as an "isoprene lamp"	Bright red heat	1	Yield of B was 30% by weight on feed	(40)

Thermal treatment of elaidic acid (isomer of oleic acid)	Special apparatus with vaporizer; attached porcelain tube containing a platinum wire heated to bright red heat, and fractionator	Bright red heat	*In vacuo*	Yield of B = ?	(40)
Decarboxylation of 2,4-pentadienoic acid (i.e., β-vinylacrylic acid or 1-carboxy-1,3-butadiene) $CH_2=CHCH=CHCOOH \rightarrow C_4H_6 + CO_2$	Catalyst: quinoline	Distillation temperature	1	Yield of B = ?	(136)

The important feature is formation of the C_5 free radicals, which would readily decarboxylate into 1,3-butadien-1-yl free radicals and then annex an atomic hydrogen.

Table 13 gives data on the conversion of carboxylic acids into butadiene.

D. MONOESTERS

Catalytic conversion of esters of 1,3-butanediol was briefly described by Ostromyslenskiǐ (132). The following equations were given for the conversions of 1,3-butanediol 3-acetate and 1,3-butanediol 1-β-hydroxybutyrate, respectively:

$$CH_2OHCH_2CH(OCOCH_3)CH_3 \rightarrow$$
$$CH_2=CH—CH=CH_2 + H_2O + CH_3COOH$$

$$CH_3CHOHCH_2COOCH_2CH_2CHOHCH_3 \rightarrow$$
$$CH_2=CH—CH=CH_2 + 2H_2O + CH_3CH=CHCOOH$$
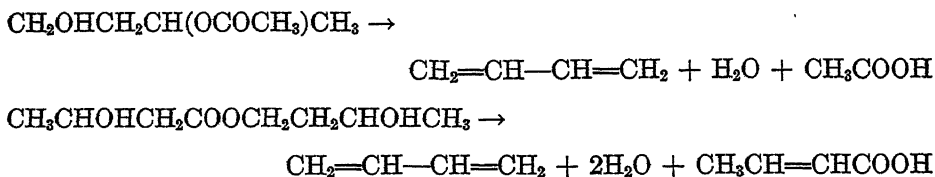
Catalytic elimination of acid from 2-buten-1-yl esters, also, will give butadiene, as demonstrated by conversions of 2-buten-1-yl acetate (126, 132) and 2-buten-1-yl trichloroacetate (155):

$$CH_3COOCH_2CH=CHCH_3 \rightarrow CH_2=CH—CH=CH_2 + CH_3COOH$$

$$CCl_3COOCH_2CH=CHCH_3 \rightarrow CH_2=CH—CH=CH_2 + CCl_3COOH$$
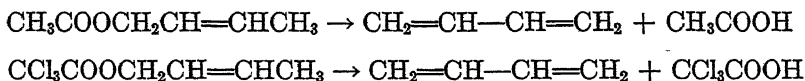
Prévost, who investigated the last reaction, maintained that it was a direct breakdown on account of overheating.

E. DIESTERS

Ostromyslenskiǐ gave the following equation for the catalytic conversion of 1,3-butanediol diacetate (126):

$$CH_3COOCH_2CH_2CH(OCOCH_3)CH_3 \rightarrow CH_2=CH—CH=CH_2 + 2CH_3COOH$$
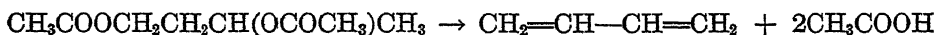
The reaction probably proceeds in two steps, possibly via both 4-acetoxy-1-butene and 1-acetoxy-2-butene. These intermediates would be favored on account of an easier removal of secondary, than primary, acetoxyl.

2,3-Butanediol diformate and diacetate form butadiene when passed at 550°C. over quartz chips (53):

$$CH_3CH(OCHO)CH(OCHO)CH_3 \rightarrow$$
$$CH_2=CH—CH=CH_2 + CO + CO_2 + H_2 + H_2O$$

$$CH_3CH(OCOCH_3)CH(OCOCH_3)CH_3 \rightarrow CH_2=CH—CH=CH_2 + 2CH_3COOH$$
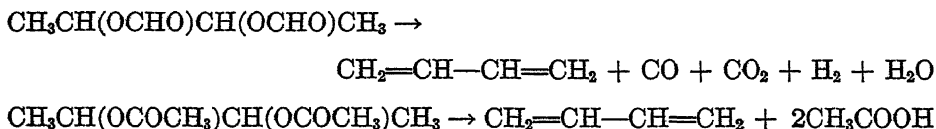
2,3-Butanediol diacetate gives butadiene at 350–575°C. over kaolin (15). The neutral sulfite of 2,3-butanediol forms butadiene at 450–575°C. over the same catalyst (15). 2,3-Butanediol diacetate undergoes an 84.9 per cent conversion into butadiene when treated thermally at about 585°C. in an atmosphere of nitro-

gen (165). Pyrolysis of the same diacetate at 595°C. and substantially atmospheric pressure forms the basis of a commercially operable process developed by the Northern Regional Research Laboratory and the Bureau of Agricultural and Industrial Chemistry of the Agricultural Research Administration, U. S. Department of Agriculture. The diacetate is obtained from 2,3-butanediol by treatment with acetic acid in the presence of sulfuric acid. A butadiene yield of 85.4 per cent of the theoretical based on butanediol charged, or 88 per cent of the theoretical based on diacetate, and a 99 per cent recovery of acetic acid have been secured (123).

Erythrite diformate, i.e., 1,2,3,4-butanetetrol diformate, was converted into butadiene at 210–220°C. by Henninger (51):

$$C_4H_6(OH)_2(OCHO)_2 \rightarrow C_4H_6 + 2CO_2 + 2H_2O$$
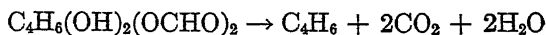
Another diester that gives butadiene is 2,3-butene bis(ethylxanthogenic acid) (174). This compound undergoes 1,2- and 3,4-eliminations without isomerization:

$$CH_3CH(-S-CS-OC_2H_5)CH(-S-CS-OC_2H_5)CH_3 \rightarrow$$

$$CH_2=CH-CH=CH_2 + 2COS + 2C_2H_5SH$$

Xanthogenates undergo elimination of an unsaturated hydrocarbon (11, 12) at relatively low temperatures because of the low bond energy of C—S linkages and the practically thermoneutral character of the over-all process. The formation of carbon oxysulfide and ethanethiol, instead of ethylxanthogenic acid, from the 2,3-butene diester, probably changes the character of the conversion f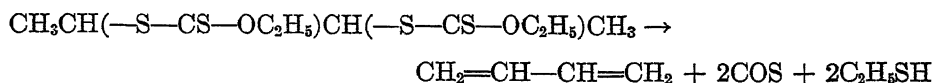rom endothermic to slightly exothermic. Development of resonance energy among the various valence-bond structures of butadiene and of carbon oxysulfide is another factor that helps overcome the endothermicity expected in elimination reactions.

F. TRIESTERS

Natural glycerides are converted into butadiene by vaporization followed by contact with a red-hot platinum wire in apparatus reminiscent of the "isoprene lamp." Olive oil, linseed oil, fish oil, and rape-seed oil are suitable (40). No explanation of the conversion of these natural products has been available to date. One can readily be given, however, based on the principle of alteration of C—C bond strengths. In the abbreviated glyceride molecule
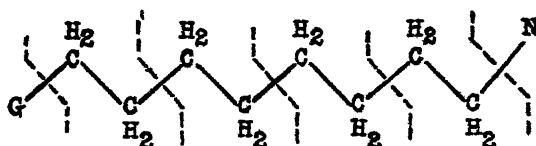
G and N represent the glyceryl and non-glyceryl ends, respectively, of a triester and its isolated group of fatty acid ethane-1,2-diyls. Thermal dehydrogenation presumably further connecting the ethanediyls at the points marked by seg-

TABLE 14

Decomposition of esters

PROCESS AND ESTER DECOMPOSED	APPARATUS AND CATALYST USED	TEMPERATURE °C.	PRESSURE atm.	REMARKS (B IS 1,3-BUTADIENE)	REFERENCES
Dehydration and deësterification of 1,3-butanediol 3-acetate (1-hydroxy-3-acetoxybutane) $CH_2OHCH_2CH(OCOCH_3)CH_3 \rightarrow C_4H_6 + H_2O + CH_3COOH$	Catalyst of undisclosed composition used; see patent disclosures (138–140) for possible data	Heated	1?	Yield of B = ?	(126)
Dehydration and deësterification of 1,3-butanediol 1-β-hydroxybutyrate (1-β-oxybutyroxy-3-hydroxybutane) $CH_3CHOHCH_2$ —O— $COCH_2CHOHCH_3$ $\xrightarrow{\ A\%\ } C_4H_6 + H_2O + CH_2CHOHCH_2COOH$ $\xrightarrow{\ 100-A\%\ } C_4H_6 + 2H_2O + CH_3CH=CHCOOH$	Catalyst of undisclosed composition used; see patent disclosures (138–140) for possible data	Heated	1?	Yield of B was 30.7% by weight on feed	(126)
Decomposition of 2-buten-1-yl acetate (crotyl acetate) $CH_3COOCH_2CH=CHCH_3 \rightarrow C_4H_6 + CH_3COOH$	Catalyst of undisclosed composition was mentioned in reference 126	Heated	1?	Yield of B = ?; see patent certificate for possible details	(126, 138)
Decomposition of 2-buten-1-yl trichloroacetate (crotyl trichloroacetate)	Sodium bromide was present; its value = ?	Heated, 140?	1	Yield of B = ?	(155)
Deësterification of 2,3-butanediol diformate (2,3-bisformoxybutane) $CH_3CH(OCHO)CH(OCHO)CH_3 \rightarrow C_4H_6 + CO + CO_2 + H_2 + H_2O$	Quartz tube packed with quartz chips	550	1	Yield of B = ?	(53)

| Reaction	Catalyst / conditions	Heated	1?	Yield of B = ?	
	Catalyst of undisclosed composition was used; see patent disclosures (138, 140) for possible data		1?	Yield of B = ?	(126)
Deësterification of 1,3-butanediol diacetate (1,3-bisacetoxybutane) CH₃COOCH₂CH₂CH(OCOCH₃)CH₃ → C₄H₆ + 2CH₃COOH	Sicromal 12 tube used	600		Yield of B was 30% by weight on fully decomposed feed	(46)
	Quartz tube	600	0.145	Yield of B was 30% by weight	(46)
		600		Yield of B was 31% by weight on fully decomposed feed	(46)
		625		Yield of B was 30.5% by weight on fully decomposed feed	(46)
	Quartz tube packed with quartz chips	550	1	Yield of B was "good" (the theoretical yield is only 31.1% by weight on feed)	(53)
	Glass tube packed with unglazed earthenware rings	510–515	1	Yield of B was 25.2% by weight on feed, corresponding to 28.9% by weight on fully decomposed feed	(53)
Deësterification of 2,3-butanediol diacetate (2,3-bisacetoxybutane) CH₃CH(OCOCH₃)CH(OCOCH₃)CH₃ → C₄H₆ + 2CH₃COOH	Glass tube packed with stainless-steel turnings	510–515?	1	Yield of B was 25.2% by weight on feed	(53)
	Catalyst: kaolin	350–575		Yield of B increased as the temperature approached 575°C.	(15)
	See reference 123 for full details	595	1	Yield of B was 27.4% by weight or 88% of the theoretical yield	(123)
	An atmosphere of nitrogen was used	585		Yield of B was 26.4% by weight or 84.9% of the theoretical yield	(105)

TABLE 14—*Continued*

PROCESS AND ESTER DECOMPOSED	APPARATUS AND CATALYST USED	TEMPERATURE	PRES-SURE	REMARKS (B IS 1,3-BUTADIENE)	REFER-ENCES
		°C.	atm.		

Decomposition of the neutral sulfite of 2,3-butanediol
 	
$CH_3CH{-}CHCH_3$
    $\mid$ $\mid \rightarrow C_4H_6 + H_2O + SO_2$
    $O{-}SO{-}O$
	Catalyst: kaolin	450–575		Yield of B was slight at 450° and 8–10% at 575°	(15)

Decomposition of 1,2,3,4-butanetetrol diformates (dihydroxybisformoxybutanes) $C_4H_6(OH)_2(OCHO)_2 \rightarrow C_4H_6 + 2CO_2 + 2H_2O$		210–220		Yield of B = ?	(51)
Decomposition of 2,3-butene bis (ethylxanthogenic acid) $CH_3CH(S{\cdot}CS{\cdot}OC_2H_5)CH(S{\cdot}CS{\cdot}OC_2H_5)CH_3 \rightarrow$ $C_4H_6 + 2COS + 2C_2H_5SH$		190–270	1	Yield of B was 5.8% by weight on feed	(174)
Thermal treatment of natural glycerides (olive oil, linseed oil, fish oil, rape-seed oil)	Special apparatus with vaporizer, attached porcelain tube containing a platinum wire heated to red heat, and fractionator	Red heat	1	Yields of B = ?	(40)
Thermal treatment of woolfat (lanolin, *Adeps lanae*) and of cholesterin and its derivatives	Vaporizer and "isoprene lamp"	Bright red heat?	?	Yield of B was considerably less than 50% by weight on feed	(41)

134

mented lines would give a molecule unsaturated at the bonds located β, ζ, κ, ξ, etc., with respect to the first methylene on the glyceryl side:
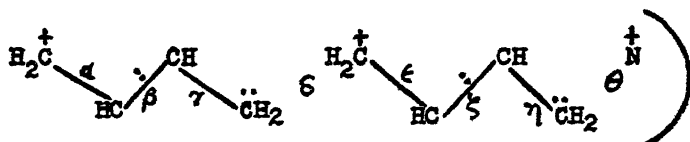
Subsequent scissions at G, N, and at the ionic bonds labelled δ, θ, μ, etc., would yield butadiene.

Table 14 gives data on the conversion of carboxylic esters into butadiene.

VI. CONCLUSION

Many organic compounds containing carbon, hydrogen, and oxygen produce butadiene under thermal or catalytic conditions. In this respect, the behavior of oxygen derivatives parallels that of the hydrocarbons. Good yields of butadiene are obtainable from ethanol, butanols, butenols, 1,3-butanediol, butanal, oleic acid, 2,3-butanediol diacetate, 4-methyl-m-dioxane, cyclohexanol, and 1,2-dihydroxybenzene. Most emphasis in the past has been on the production of butadiene in one stage, as in the cases of ethanol and 3-methyl-1-butanol.

REFERENCES

(1) BALANDIN, A. A.: Acta Physicochim. U.R.S.S. **2**, 345–62 (1935) (in English).
(2) BALANDIN, A. A.: Acta Physicochim. U.R.S.S. **2**, 363–76 (1935) (in English); J. Phys. Chem. (U.S.S.R.) **6**, 357 (1935).
(3) BENNETT, G. M., AND HEATHCOAT, F.: J. Chem. Soc. **1929**, 268–74.
(4) BOITEAU, G.: British patent 15,806 (July 2, 1914) (void).
(5) BOUVEAULT, L., AND LOCQUIN, R.: Bull. soc. chim. [3] **35**, 643–6 (1906).
(6) BUIZOV, B. V.: Russian patent 1101 (September 15, 1925); Chem. Abstracts **22**, 4132 (1928).
(7) CAVENTOU, E.: Compt. rend. **56**, 646–8 (1863); Ann. **127**, 93–7 (1863).
(8) CHALMERS, W.: German patent 599,503 (July 11, 1935); Chem. Zentr. **1935**, II, 2281.
(9) CHARON, E.: Ann. chim. phys. [7] **17**, 217 (1899).
(10) CHARON, E.: Ann. chim. phys. [7] **17**, 234 (1899).
(11) CHUGAEV, L. A.: Ber. **32**, 3332–5 (1899); **33**, 735–6, 3118–26 (1900); **35**, 2473–83 (1902); **37**, 1481–6 (1904); J. Russ. Phys.-Chem. Soc. **31**, 959–61, 961–2 (1899); **32**, 79–80, 358–60 (1900); **35**, 1116–79 (1903); **36**, 988–1052 (1904); Russian dissertation: "Research on Terpenes and Camphor," Moscow (1903).
(12) CHUGAEV, L. A., AND FOMIN, V.: Ann. **375**, 288–97 (1910).
(13) CIAMICIAN, G., AND MAGNAGHI, P.: Ber. **19**, 569–74 (1886).
(14) CIAMICIAN, G., AND SILBER, P.: Ber. **48**, 190–5 (1915).
(15) DENIVELLE, L.: Compt. rend. **208**, 1024–5 (1939).
(16) DEUX, Y.: Compt. rend. **207**, 920–1 (1938).
(17) DEUX, Y.: Compt. rend. **208**, 1090–2 (1939).
(18) DEWEY, COL. B.: "Progress Report No. 5, March 17, 1944," United States of America, War Production Board, Office of Rubber Director, Washington, D. C.
(19) DOYARENKO, M. N.: Ber. **60**, 1536–53 (1927); J. Russ. Phys.-Chem. Soc. **58**, 16–26 (1926).
(20) DOYARENKO, M. N.: J. Russ. Phys.-Chem. Soc. **58**, 27–38 (1926).

(21) EGLOFF, G., AND HULLA, G.: Chem. Rev. **35**, 279–333 (1944).

(22) EGLOFF, G., AND HULLA, G.: Oil Gas J. **41**, No. 29, 127 (1942).

(23) EGLOFF, G., AND HULLA, G.: Oil Gas J. **41**, No. 31, 45–51 (1942).

(24) EGLOFF, G., AND HULLA, G.: Oil Gas J. **41**, No. 32, 36–8 (1942).

(25) EGLOFF, G., HULLA, G., AND KOMAREWSKY, V. I.: *Isomerization of Pure Hydrocarbons*, pp. 55–6, 244–5. American Chemical Society Monograph No. 88. Reinhold Publishing Corporation, New York (1942).

(26) FARBENFABRIKEN VORM. FRIEDR. BAYER AND Co.: British patent 4,076 (October 16, 1913).

(27) FARBENFABRIKEN VORM. FRIEDR. BAYER AND Co.: British patent 27,555 (August 17, 1911).

(28) FARBENFABRIKEN VORM. FRIEDR. BAYER AND Co.: French patent 425,967 (February 18, 1911); French patent of addition 17,873 (June 17, 1913); German patents 241,895 (March 12, 1910) and 262,884 (July 26, 1912).

(29) FARBENFABRIKEN VORM. FRIEDR. BAYER AND Co.: German patent 262,553 (July 11, 1913); Friedlaender's Fortschritte der Teerfarbenfabrikation **11**, 822 (1915).

(30) FARBENFABRIKEN VORM. FRIEDR. BAYER AND Co.: German patent 263,016 (April 14, 1913); Friedlaender's Fortschritte der Teerfarbenfabrikation **11**, 797 (1915).

(31) FARBENFABRIKEN VORM. FRIEDR. BAYER AND Co.: German patent 263,066 (April 14, 1913); Friedlaender's Fortschritte der Teerfarbenfabrikation **11**, 796 (1915).

(32) FARBENFABRIKEN VORM. FRIEDR. BAYER AND Co.: German patent 264,264 (April 28, 1913); Friedlaender's Fortschritte der Teerfarbenfabrikation **11**, 797–8 (1915).

(33) FARBENFABRIKEN VORM. FRIEDR. BAYER AND Co.: German patent 278,647 (June 11, 1914); Friedlaender's Fortschritte der Teerfarbenfabrikation **12**, 564–5 (1917).

(34) FILIPPOV, O. G.: J. Russ. Phys.-Chem. Soc. **42**, 364–5 (1910); Translation S-244, Universal Oil Products Company (J. G. Tolpin) Survey of Foreign Petroleum Literature. [This survey will be designated hereafter as U.O.P. Co. Survey Foreign Petroleum Literature.]

(35) FILIPPOV, O. G.: *Preparation of Butadiene by Contact Pyrolysis*, page 79 (1914); cf. reference 95.

(36) FRIEDRICHSEN, W., AND FITZKY, W. (assignors to General Aniline and Film Corporation): U. S. patent 2,218,640 (October 22, 1940).

(37) FULMER, E. I.: Contributions from Iowa Corn Research Institute **3**, No. 1, 62 pp. (1943).

(38) GAMMA, J. A., AND INOUYE, T.: Chem. & Met. Eng. **49**, No. 12, 97–100 (1942).

(39) GDANOVITCH: J. Russ. Phys.-Chem. Soc. **36**, 765 (1904).

(40) GERLACH, A., AND KOETSCHAU, R.: German patent 267,079 (July 21, 1913); Friedlaender's Fortschritte der Teerfarbenfabrikation **11**, 825–7 (1915).

(41) GERLACH, A., AND KOETSCHAU, R.: German patent 267,080 (July 21, 1913); Friedlaender's Fortschritte der Teerfarbenfabrikation **11**, 827 (1915).

(42) GILLILAND, E. R.: Sci. Monthly **58**, 5–15 (1944).

(43) GORIN, YU. A., NEIMARK, O. M., AND KOGAN, F. N.: Sintet. Kauchuk **4**, No. 5, 6–10 (1935); Translation S-199, U.O.P. Co. Survey Foreign Petroleum Literature.

(44) GRÉDY, B., AND PIAUX, L.: Bull. soc. chim. [5] **1**, 1481–9 (1934).

(45) GRÉDY, B., AND PIAUX, L.: Compt. rend. **198**, 1235–7 (1934).

(46) GUGGEMOS, H., AND TREIBS, A. (vested in the Alien Property Custodian): U. S. patent 2,345,113 (March 28, 1944).

(47) GUINOT, H. M. (assignor to Usines de Melle): U. S. patent 2,237,866 (April 8, 1941).

(48) GUTNER, R., AND TISHCHENKO, D.: J. Gen. Chem. (U.S.S.R.) **6**, 1729–36 (1936); Translation S-307A, U.O.P. Co. Survey Foreign Petroleum Literature.

(49) HAGEMANN, A.: Z. angew. Chem. **42**, 355–61 (1929).

(50) HALBIG, P., PLATZER, N., AND TREIBS, A.: U. S. patent 2,229,652 (January 28, 1941). CONSORTIUM FÜR ELEKTROCHEMISCHE INDUSTRIE G.M.B.H.: British patent 524,849 (August 15, 1940) and French patent 850,070 (December 7, 1939).

(51) Henninger, A.: Ann. chim. [6] 7, 209–33, especially p. 211 (1886).

(52) Henninger, A.: Ber. 6, 70–1 (1873).

(53) Hill, R., Isaacs, E., and Imperial Chemical Industries Ltd.: British patent 483,989 (April 28, 1938).
Hill, R., and Isaacs, E.: U. S. patent 2,224,912 (December 17, 1940).

(54) Hofmann, F., and Tank, L. (assignors to Farbenfabriken vorm. Friedr. Bayer and Co.): U. S. patent 1,010,405 (November 28, 1911).

(55) Huntenburg, W.: German patent 661,902 (June 30, 1938); Chem. Zentr. 1938, II, 2843; Chem. Abstracts 32, 8443-4 (1938).

(56) Huntenburg, W.: J. prakt. Chem. [2] 145, 23–30 (1936).

(57) Huntenburg, W.: Über die Reaktionsprodukte aus Crotonaldehyd und Ammoniak,'¹ Dissertation, Hamburg, 1929.

(58) I. G. Farbenindustrie A.-G.: British patent 326,185 (February 27, 1930).

(59) I. G. Farbenindustrie A.-G.: British patent 345,270 (March 18, 1931).

(60) I. G. Farbenindustrie A.-G.: British patent 505,904 (May 17, 1939); Chem. Abstracts 33, 9328 (1939).

(61) I. G. Farbenindustrie A.-G.: British patent 506,038 (May 18, 1939); Chem. Abstracts 33, 9328 (1939).

(62) I. G. Farbenindustrie A.-G.: British patent 506,674 (June 2, 1939); Chem. Abstracts 33, 9328 (1939).

(63) I. G. Farbenindustrie A.-G.: French patent 844,893 (August 3, 1939); Chem. Abstracts 34, 7931 (1941).

(64) I. G. Farbenindustrie A.-G.: French patent 845,305 (August 18, 1939); Chem. Abstracts 35, 1068 (1941).

(65) I. G. Farbenindustrie A.-G.: German patent application I. 36212; Friedlaender's Fortschritte der Teerfarbenfabrikation 17, 140 (1932).

(66) I. G. Farbenindustrie A.-G. (R. Leopold and A. Michael, inventors): German patent 507,995 (September 23, 1930).

(67) I. G. Farbenindustrie A.-G. (M. Mueller-Cunradi and E. Ober, inventors): German patent 522,148 (November 14, 1929); Friedlaender's Fortschritte der Teerfarbenfabrikation 16, 2979 (1931).

(68) I. G. Farbenindustrie A.-G. (F. Runge, and M. Mueller-Cunradi, inventors): German patent 578,038 (June 12, 1933).

(69) I. G. Farbenindustrie A.-G.: German patent 696,779 (August 29, 1940).

(70) I. G. Farbenindustrie A.-G.: German patent 700,036 (November 14, 1940); Chem. Abstracts 35, 6982-3 (1941).

(71) Ipatieff, V. N.: Ber. 35, 1047–57 (1902); J. Russ. Phys.-Chem. Soc. 34, 182–95 (1902).

(72) Ipatieff, V. N.: Ber. 36, 1990–2003 (1903).

(73) Ipatieff, V. N.: Catalytic Reactions at High Pressures and Temperatures, pp. 20–21. The Macmillan Co., New York (1936).

(74) Reference 73, pp. 119–20.

(75) Ipatieff, V. N.: Chem.-Ztg. 26, 530 (1902).

(76) Ipatieff, V. N.: J. prakt. Chem. [2] 67, 420–2 (1903); J. Russ. Phys.-Chem. Soc. 35, 449–52 (1903); Translation S-243, U.O.P. Co. Survey Foreign Petroleum Literature.

(77) Ipatieff, V. N.: Private communication.

(78) Istituto per lo Studio Della Gomma Sintetica, Maximoff, A., and Canonici, O.: British patent 535,678 (April 17, 1941).

(79) Kanbara, S.: J. Soc. Chem. Ind. Japan 43, Suppl. binding 262b-263b (1940); Chem. Abstracts 35, 4993 (1941).

(80) Kirner, W. R., and Richter, G. H.: J. Am. Chem. Soc. 51, 2503–6 (1929).

(81) Komarewsky, V. I., and Stringer, J. T.: J. Am. Chem. Soc. 63, 921–2 (1941).

(82) Krause, V. P., Kogan, A. M., and Kozlovskaya, A. V.: Trudy Gosurdarst. Opyt. Zavoda Sintet. Kauchuka, Litera B, 3, 50–68 (1934); Chem. Abstracts 30, 4810–11 (1936).

(83) KRAUSE, V. P., AND SLOBODIN, YA. M.: J. Applied Chem. (U.S.S.R.) 9, 1278–89 (1936); Translation S-188, U.O.P. Co. Survey Foreign Petroleum Literature.

(84) KYRIAKIDES, L. P.: J. Am. Chem. Soc. 36, 980–7 (1914).

(85) KYRIAKIDES, L. P., AND EARLE, R. B.: U. S. patent 1,033,327 (July 23, 1912).

(86) LEBEDEV, S. V.: British patent 331,482 (June 30, 1930).

(87) LEBEDEV, S. V.: French patent 665,917 (December 15, 1928).

(88) LEBEDEV, S. V.: German patent 577,630 (June 3, 1933).

(89) LEBEDEV, S. V.: J. Gen. Chem. (U.S.S.R.) 3, 698–717 (1933); Trans. Experimental Plant "B" 3, (1933); "S. V. Lebedev, Life and Works," O.N.T.I. Khimteoret, Leningrad (1938), pp. 491–514; Translation S-183, U.O.P. Co. Survey Foreign Petroleum Literature.

(90) LEBEDEV, S. V.: Polish patent 16,966 (February 12, 1929); Chem. Zentr. 1933, II, 3916.

(91) LEBEDEV, S. V.: Russian patent 24,393 (September 24, 1931); Chem. Abstracts 28, 3050 (1934).

(92) LEBEDEV, S. V.: Russian patent 35,182 (March 31, 1934).

(93) LEBEDEV, S. V.: Sotzialist. Rekonstruktziya i Nauka 3, No. 1, 127–36 (1933); Chem. Abstracts 29, 2390–1 (1935).

(94) LEBEDEV, S. V.: Teknicheskaya Entsiklopediya (Technical Encyclopedia) 20, 815 ff. (1935); "S. V. Lebedev, Life and Works," O.N.T.I. Khimteoret, Leningrad (1938), pp. 443–61; Translation S-171, U.O.P. Co. Survey Foreign Petroleum Literature.

(95) LEBEDEV, S. V., GORIN, YU. A., KHUTORETSKAYA, S. N., CHARSKAYA, K. N., AND KOGAN, F. N.: Sintet. Kauchuk 4, No. 1, 8–27 (1935); "S. V. Lebedev, Life and Works," O.N.T.I. Khimteoret, Leningrad (1938), pp. 602–23; Translation S-185, U.O.P. Co. Survey Foreign Petroleum Literature.

(96) LEBEDEV, S. V., KOBLYANSKIĬ, G. G., ANDREEV, N. Z., GORN, I. K., LIVSHITZ, I. A., SIBIRYAKOVA, G. N., AND SLOBODIN, YA. M.: Trudy Gosudarst. Opyt. Zavoda Sintet. Kauchuka, Litera B, 3, 41–4 (1934); Chem. Abstracts 30, 4810 (1936).

(97) LEBEDEV, S. V., KOBLYANSKIĬ, G. G., ANDREEV, N. Z., VOLZHINSKIĬ, I. A., GORIN, YU. A., GORN, I. K., KIBIRKSHTIS, S. S., SIBIRYAKOVA, G. N., AND SLOBODIN, YA. M.: Trudy Gosudarst. Opyt. Zavoda Sintet. Kauchuka, Litera B, 3, 44–50 (1934); Chem. Abstracts 30, 4810 (1936).

(98) LEBEDEV, S. V., AND SKAVRONSKAYA, N. A.: J. Russ. Phys.-Chem. Soc. 43, 1124–31 (1911); Chem. Abstracts 6, 855 (1912).

(99) LEBEDEV, S. V., VOLZHINSKIĬ, I. A., GORIN, YU. A., GULYAEVA, A. I., KOGAN, G. M., KIBIRKSHTIS, S. G., KOBLYANSKIĬ, G. G., KRAUSE, V. P., KRUPUISHEV, M. A., LIVSCHITZ, I. A., ORLOV, S. M., SLOBODIN, YA. M., SUBBOTIN, S. A., KHOKHLOVKIN, M. A., RESHETOV, A. N., AND TATARNIKOV, A. M.: Trudy Gosudarst. Opyt. Zavoda Sintet. Kauchuka, Litera B, 3, 16–40 (1934); "S. V. Lebedev, Life and Works," O.N.T.I. Khimteoret, Leningrad (1938), pp. 526–53; Translation S-191, U.O.P. Co. Survey Foreign Petroleum Literature.

(100) LEBEDEV, S. V., VOLZHINSKIĬ, I. A., KIBIRKSHTIS, S. G., KOBLYANSKIĬ, G. G., KRAUSE, V. P., KRUPYSHEV, M. A., AND SLOBODIN, YA. M.: Trudy Gosudarst. Opyt. Zavoda Sintet. Kauchuka, Litera B, 3, 7–16 (1934); "S. V. Lebedev, Life and Works," O.N.T.I. Khimteoret, Leningrad (1938), pp. 515–25; Translation S-192, U.O.P. Co. Survey Foreign Petroleum Literature.

(101) LENNARD-JONES, J. E., AND TURKEVICH, J.: Proc. Roy. Soc. (London) A158, 297–305 (1937).

(102) LEYES, C. J.: British patent 329,748 (May 20, 1930).

(103) LEYES, C. J.: French patent 672,210 (December 24, 1929).

(104) LEYES, C. J.: German patent 569,343 (December 3, 1931); Friedlaender's Fortschritte der Teerfarbenfabrikation 18, 138–40 (1933).

(105) LEYES, C. J.: U. S. patent 1,884,002 (October 25, 1932).

(106) LIEBEN, A., AND ZEISEL, S.: Monatsh. **1**, 823,840 (1880).

(107) LIKHOSHERSTOV, M. V., CHIFINA, L. F., AND KUTEPOV, E. F.: Acta Univ. Voronegiensis **8**, No. 4, 81–5 (1935); Chem. Abstracts **32**, 6616 (1938).

(108) LIVSCHITZ, I. A., AND SINAÏSKIÏ, G. M.: Sintet. Kauchuk **5**, No. 6, 17–21 (1936); Translation S-238, U.O.P. Co. Survey Foreign Petroleum Literature.

(109) MATTHEWS, F. E., STRANGE, E. H., AND BLISS, H. J. W.: British patent 3873 (March 17, 1913).

(110) MATTHEWS, F. E., STRANGE, E. H., AND BLISS, H. J. W.: British patent 12,771 (May 30, 1913).

(111) MAXIMOFF, A. T. (assignor to Naugatuck Chemical Co.): U. S. patent 1,682,919 (September 4, 1928).

(112) MERESHKOVSKIÏ, B. K.: Bull. soc. chim. [4] **37**, 1174–87 (1925).

(113) MULLIKEN, R. S.: J. Chem. Phys. **7**, 121–35, 364–73 (1939); Rev. Modern Phys. **14**, 265–74 (1942).

(114) MURPHY, W. J.: Chemical Industries **50**, No. 2, Pt. 1, 172 (1942).

(115) NAGAI, N.: J. Soc. Chem. Ind. Japan **44**, Suppl. binding 64b–66b (1941).

(116) NEF, J. U.: Ann. **318**, 137–230, especially p. 201 (1901).

(117) Reference 116, especially pp. 206-7.

(118) Reference 116, especially p. 208.

(119) Reference 116, especially pp. 208–9.

(120) Reference 116, especially p. 215.

(121) Reference 116, especially p. 218.

(122) Reference 116, especially pp. 223–4.

(123) NORTHERN REGIONAL RESEARCH LABORATORY AND THE BUREAU OF AGRICULTURAL AND INDUSTRIAL CHEMISTRY, AGRICULTURAL RESEARCH ADMINISTRATION, U. S. DEPARTMENT OF AGRICULTURE: "The Development of a Process for the Manufacture of 1,3-Butadiene from 2,3-Butylene Glycol," July 15, 1943.

(124) OBOLENTSEV, R., PAZHITNOV, B., RUTKOVSKIÏ, R., AND TRIFEL, A.: Neftyanaya Prom. (Petrol. Ind. U.S.S.R.) **1941**, No. 1, pp. 93–9; Khim. Referat. Zhur. **4**, No. 9, 119 (1941); abstract translated in July 10, 1942, U.O.P. Co. Survey Foreign Petroleum Literature.

(125) OSTROMYSLENSKIÏ, I. I.: J. Russ. Phys.-Chem. Soc. **46**, 1737–8 (1914).

(126) OSTROMYSLENSKIÏ, I. I.: J. Russ. Phys.-Chem. Soc. **47**, 1472–94 (1915); Translation S-152, U.O.P. Co. Survey Foreign Petroleum Literature.

(127) OSTROMYSLENSKIÏ, I. I.: J. Russ. Phys.-Chem. Soc. **47**, 1472–94 (1915); Translation S-152, p. 7, U.O.P. Co. Survey Foreign Petroleum Literature.

(128) OSTROMYSLENSKIÏ, I. I.: J. Russ. Phys.-Chem. Soc. **47**, 1472–94 (1915); Translation S-152, p. 14, U.O.P. Co. Survey Foreign Petroleum Literature.

(129) OSTROMYSLENSKIÏ, I. I.: J. Russ. Phys.-Chem. Soc. **47**, 1494–1506 (1915); Translation S-157, U. O. P. Co. Survey Foreign Petroleum Literature.

(130) OSTROMYSLENSKIÏ, I. I.: J. Russ. Phys.-Chem. Soc. **47**, 1947–78 (1915); Chem. Abstracts **10**, 1340–1 (1916).

(131) OSTROMYSLENSKIÏ, I. I.: J. Russ. Phys.-Chem. Soc. **47**, 1978–82 (1915); Chem. Abstracts **10**, 1341 (1916); Chem. Zentr. **1916**, II, 307.

(132) OSTROMYELENSKIÏ, I. I.: J. Russ. Phys.-Chem. Soc. **47**, 1991–3 (1915); Chem. Abstracts **10**, 1342 (1916).

(133) OSTROMYSLENSKIÏ, I. I.: "Kauchuk i Ego Analogi," Moscow (1913), pp. 177–80; Translation S-245, U.O.P. Co. Survey Foreign Petroleum Literature.

(134) OSTROMYSLENSKIÏ, I. I.: "Kauchuk i Ego Analogi," Moscow (1913), pp. 195–204; cf. reference 126.

(135) OSTROMYSLENSKIÏ, I. I.: "Kauchuk i Ego Analogi," Moscow (1913); Translation S-201A, p. 44, U.O.P. Co. Survey Foreign Petroleum Literature.

(136) OSTROMYSLENSKIÏ, I. I.: "Kauchuk i Ego Analogi," Moscow (1913); Translation S-201A, p. 47, U.O.P. Co. Survey Foreign Petroleum Literature.

(137) OSTROMSYLENSKIĬ, I. I.: "Kauchuk i Ego Analogi," Moscow (1913); Translation S-201A, p. 49, U.O.P. Co. Survey Foreign Petroleum Literature.
(138) OSTROMYSLENSKIĬ, I. I.: Russian patent certificate 65,122 (October 16, 1914).
(139) OSTROMYSLENSKIĬ, I. I.: Russian patent certificate 65,391 (December 3, 1914).
(140) OSTROMYSLENSKIĬ, I. I.: Russian privilege 25,590, application of February 29, 1912.
(141) OSTROMYSLENSKIĬ, I. I.: Zemledel'cheskaya Gazeta (Agr. Gaz. Petrograd) 1915, Nos. 25–26, 701–6, 727–8; Monthly Bull. Agr. Intelligence 12, 1701–3 (1915).
(142) OSTROMYSLENSKIĬ, I. I., AND KELBASINSKIĬ, S. S.: J. Russ. Phys.-Chem. Soc. 46, 123–33 (1914); Chem. Abstracts 8, 1965 (1914).
(143) OSTROMYSLENSKIĬ, I. I., AND KELBASINSKIĬ, S. S.: J. Russ. Phys.-Chem. Soc. 47, 1509–29 (1915); Translation S-166, U.O.P. Co. Survey Foreign Petroleum Literature.
(144) OSTROMYSLENSKIĬ, I. I., AND RABINOVICH, P. N.: J. Russ. Phys.-Chem. Soc. 47, 1507–9 (1915); Translation S-158, U.O.P. Co. Survey Foreign Petroleum Literature.
(145) PASCAL, P. V. H.: British patent 140,115 (March 25, 1920 (accepted)).
(146) PATERNÒ, E., CHIEFFI, G., AND PERRET, G.: Gazz. chim. ital. 44, I, 151–64 (1914).
(147) PAULING, L.: The Nature of the Chemical Bond, 2nd edition, pp. 53, 131. Cornell University Press, Ithaca, New York (1940).
(148) PENNEY, W. G.: Proc. Roy. Soc. (London) A146, 223–38 (1934).
(149) PERKIN, W. H., AND MATTHEWS, F. E.: British patent 17,235 (July 24, 1913 (accepted)).
(150) PETRENKO, A. V.: Kauchuk i Rezina 1940, No. 4–5, 1–5; Translation S-230, III, U.O.P. Co. Survey Foreign Petroleum Literature.
(151) PETROV, A. A.: Trans. Voronezh State University 10, No. 2, 101–83 (1938); Translation S-165, U.O.P. Co. Survey Foreign Petroleum Literature.
(152) PLAUSON, H., AND VIELLE, J. A.: British patent 156,145 (December 31, 1920).
(153) PRÉVOST, C.: Ann. chim. [10] 10, 113–46 (1928).
(154) PRÉVOST, C.: Ann. chim. [10] 10, 147–81 (1928).
(155) PRÉVOST, C. Ann. chim. [10] 10, 147–81 (1928); cf. reference 153.
(156) PRÉVOST, C. Ann. chim. [10] 10, 356–439 (1928).
(157) PRÉVOST, C. Compt. rend. 186, 1209–11 (1928).
(158) PRICE, W. C., AND WALSH, A. D.: Proc. Roy. Soc. (London) A174, 220–34 (1940).
(159) RASMUSSEN, R. S., TUNNICLIFF, D. D., AND BRATTAIN, R. R.: J. Chem. Phys. 11, 432–3 (1943).
(160) REPPE, W. (assignors to General Aniline and Film Corporation): U. S. patent 2,251, 292 (August 5, 1941); Chem. Abstracts 35, 6982 (1941).
(161) REPPE, W., HECHT, O., AND STEINHOFER, A. (assignors to General Aniline and Film Corporation): U. S. patent 2,251,895 (August 5, 1941).
(162) REPPE, W., STEINHOFER, A., AND DAUMILLER, G.: U. S. patent 2,310,809 (February 9, 1943).
(163) REPPE, W., STEINHOFER, A., AND HECHT, O. (assignors to General Aniline and Film Corporation): U. S. patent 2,241,792 (May 13, 1941).
(164) REPPE, W., AND TRIESCHMANN, H. G. (assignors to General Aniline and Film Corporation): U. S. patent 2,251,835 (August 5, 1941); Chem. Abstracts 35, 7421 (1941).
(165) SCHLECHTER, N., OTHMER, D. F., AND BRAND, R.: Paper presented before the Division of Industrial and Engineering Chemistry, 108th Meeting of the American Chemical Society, New York, September 11–15, 1944.
(166) SHILOV, E. A.: Sintet. Kauchuk 1, No. 2, 5–12 (1932); Translation S-234, U.O.P. Co., Survey Foreign Petroleum Literature.
(167) SLOBODIN, YA. M.: J. Gen. Chem. (U.S.S.R.) 5, 1415–20 (1935); Translation S-195, U.O.P. Co. Survey Foreign Petroleum Literature.
(168) SMIRNOV, N. I.: Sintet. Kauchuk 3, No. 1, 13–22 (1934); Translation S-236, U.O.P. Co. Survey Foreign Petroleum Literature.
(169) STAUDINGER, H., ENDLE, R., AND HEROLD, J.: Ber. 46, 2466–77 (1913).

(170) TALALAY, A., AND TALALAY, L.: Rubber Chem. Tech. **15**, 403–29 (1942).

(171) THIELE, J.: Ann. **308**, 333–43 (1899).

(172) TIFFENEAU, M., LÉVY, J., AND WEILL, P.: Bull. soc. chim. [4] **49**, 1606–17, especially pp. 1607–8 (1931).

(173) TIFFENEAU, M., AND WEILL, P.: Compt. rend. **204**, 590–92 (1937).

(174) TISCHENKO, V. S., AND KOSTERNAYA, A. F.: J. Gen. Chem. (U.S.S.R.) **7**, 1366–77 (1937).

KOSTERNAYA, A. F.: Uchenye Zapiski Leningrad. Gosudarst. Univ., Ser. Khim. Nauk **3**, 126–56 (1938); Translation S-216A, U.O.P. Co. Survey Foreign Petroleum Literature.

(175) URION, E.: Ann. chim. [11] **1**, 5–87 (1934).

(176) URION, E.: Ann. chim. [11] **1**, 5–87 (1934); *cf.* URION, E.: Compt. rend. **196**, 353–4 (1933).

(177) URION, E., AND BAUM, E.: Compt. rend. **204**, 595–7 (1937).

(178) WELLMAN, V. E. (assignor to The B. F. Goodrich Co.): U. S. patent 2,174,280 (September 26, 1939).

(179) WHELAND, G. W.: J. Chem. Phys. **2**, 474–81 (1934).

(180) WHELAND, G. W.: Proc. Roy. Soc. (London) **A164**, 397–408 (1938).

(181) YOUNG, W. G., AND WINSTEIN, S.: J. Am. Chem. Soc. **57**, 2013 (1935).

(182) ZAĬTSEV, A. M.: Ann. **179**, 296–301 (1875).

ERRATA

Volume 33, Number 2, October, 1943

Page 162: In the fifth line from the bottom of the page read "Ca[Ni(CN)$_4$]5H$_2$O" for "Ba[Ni(CN)$_4$]4H$_2$O".

In the fourth line from the bottom of the page read "perpendicular" for "parallel".

Page 170: In the thirteenth line read "the use of *dsp*^{2} orbitals" for "the use of orbitals". In the last line (exclusive of the footnote) read "Pt^{++}" for "Pt^{II}".

Volume 35, Number 2, October, 1944

Page 85: In Section G benzimino ethyl ether should be described as an ammono aquo acid ester.

Page 91: In the fifth line from the bottom read "2,6-dimethyl-γ-pyridone" for "2,3-dimethyl-γ-pyridone".

Page 108: In the third line of the second paragraph in Section D read "these are" for "pyridine is".

Page 114: The fourth line below equation 21 should read, "amides that prevented further reaction, to lack of reaction, or to the retention of ammonia by the ..."

Page 119: In the first line below equation 29 read "(2-pyridylmethyl)" or "(2-picolyl)" for "(2-pyridyl)".

Page 125: In the fifth line the word before "promoting" should be "in".

Page 136: In the second line of the paragraph beginning "Nitration" delete the first "aquo".

Page 143: In the seventh line read "alcoholic" for "alcholic".

Page 149: The subheading should read "Expanded cyclic aquo hemiacetals: xanthydrol".

Page 153: In formula VI delete the subscript 2 of the top CH$_2$ group.

Page 156: In Section 6 add reference 161.

Page 161: In the first line of paragraph (c) read "observed".

Page 162: In the first and second lines of the text read "quinoline" for "quinaldine".

Page 168: In the fourteenth line of the first paragraph read "benzoyl" for "benzyol".

Page 175: In the sixth line above Section J read "2-alkoxyquinoline-4-carboxylic acid derivatives" for "2-alkoxyquinoline-4-carboxylic acids". In the eleventh line above Section J delete "aquo".

Page 176: The second sentence in the second paragraph should read, "The sodium salt of its reduction product ..."

Page 180: In the fifth line below equation 83 read "nitrostyrylquinoline" for "nitrostyrylquinaldine".

Page 182: In the sixth line from the bottom read "4-methyl-2-(β,β'-dihydroxyiso-propyl)quinoline" for "4-methyl-2-(β,β-dihydroxyisopropyl)quinoline".

Page 183: In the third line read "2,4-di(2',4'-dinitrostyryl)" for "2,4-di(2,4-dinitrostyryl)".

Page 186: The N in the lower left-hand corner of the middle formula of equation 95 is not printed clearly.

Page 196: In the second line of the text read "*p*-dimethylaminobenzaldehyde" for "*p*-aminobenzaldehyde".

Page 210: In the thirteenth line read "added to the 4-position of" for "added to the 1,4-positions of". In the third line below formula XVI read "adds to the 4-position of" for "adds in the 1,4-position to".

Page 213: In equation 137 read "$3C_2H_5OH$" for "$2C_2H_5OH$".

Page 215: In the eighth line read "α-bromo-β-anilinoacrylaldehyde anil" for "α-bromo- and β-anilinoacrylaldehyde anil".

Page 219: In the last line read "$-CH(OC_2H_5)_2$" for "$-CH(COOC_2H_5)$".

Page 220: In the second line in Section 3 read "aminomethylphenylcarbinol ethers" for "aminophenylcarbinol ethers".

Page 231: In the first line of the second paragraph read "isoquinolinium salt" for "quinolinium salt". In formulas I and II the methyl groups should be attached to nitrogen.

Page 234: In the second line read "1-iodoisoquinoline" for "1-iodoquinoline".

In the last line of the first paragraph in Section H read "$R\overset{|}{C}=N-$" for "$R\overset{|}{C}=M-$".

Page 261: In reference 410 the pages should be 3130–1.

Page 271: Reference 665 was omitted:

(665) German patent 576,532 (May 17, 1933); Chem. Abstracts **27,** 5896 (1933).

Page 273: To reference 702c add "Ber. **48,** 1465–6, 1470–2(1915); see reference 609b".

Page 274: In reference 752 read "Agliardi" for "Agliadir".

Page 283: In the second line of the fifth paragraph read "allyl compounds" for "alkyl compounds".

Page 287: In the second line of the paragraph beginning "In the . . ." read "ethene is a reaction product" for "ethane is a reaction product".

HYPERCONJUGATION

CLARA L. DEASY

Department of Chemistry, University of Illinois, Urbana, Illinois

CONTENTS

I. INTRODUCTION

During the past decade the concept of hyperconjugation has been employed in organic chemistry and in closely related fields to explain and to correlate a variety of experimental data. Although some of the ideas regarding specific detail are still in a state of flux, a review to indicate the wide applicability of the subject seems warranted at the present time.

II. THE CONCEPT OF HYPERCONJUGATION

The manner of definition of the term *hyperconjugation* depends primarily upon the particular method of approach to the problem. There are now in use three essentially different presentations of the concept, with resulting differences in terminology and, to some extent, in detail.

In England, Baker and Nathan (10) were the first explicitly[1] to put forth the concept of hyperconjugation in order to explain the abnormal behavior of certain series of alkyl-substituted compounds; hence in the English literature hyperconjugation is often referred to as the *Baker–Nathan effect*. In a paper in 1935 they suggested that the duplet of electrons forming the carbon–hydrogen bond of an alkyl group which is attached to an unsaturated carbon atom is less localized than that in a similar carbon–carbon bond; hence electron release is permitted by a mechanism which is essentially a type of tautomeric effect:

$$H \overparen{-CH_2 \overparen{-C} = \overparen{C}-}$$

---
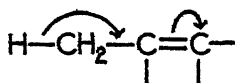
[1] For earlier work pointing in the same direction, however, see references 13, 14, and 39.

It should be noted that the postulated effect acts in addition to, and in the same direction as, the inductive effect of alkyl groups. The latter effect, however, increases in strength in the sequence methyl $<$ ethyl $<$ isopropyl $<$ tertiary butyl; but the hyperconjugation effect would be expected to decrease in the order methyl $>$ ethyl $>$ isopropyl $>$ tertiary butyl, if one assumes with Baker and Nathan that only the α-hydrogen atoms of the group are effective.

From the viewpoint of quantum mechanics two methods of approach which are less restricted in application have been used. According to one, hyperconjugation is considered to result from the contribution to the resonance hybrid of structures closely related to those occurring in conjugated systems:

$$H^+ \quad CH_2{=}\overset{-}{C}{-}\overset{\cdot}{C}{-} \qquad H\cdot \quad CH_2{=}\overset{\cdot}{C}{-}\overset{\cdot}{C}{-}$$

Such structures are believed to make small but definite contributions to the ground state of the molecule[2] (38, 43).

The second point of view, supported by quantum-mechanical calculations using the molecular orbital method, assumes that systems such as the following, which contain an unsaturated center, exhibit a kind of conjugation:

$$H_3{\equiv}C{-}\underset{\cdot}{C}{=}C{-}$$
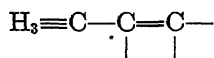
The quasi-triple bond, $H_3{\equiv}C$, is considered to be analogous to an ordinary triple bond, and therefore a conjugation will be present over and above that ordinarily recognized: hence the term *hyperconjugation* (36).

In this method of presentation, a quasi-triple bond is considered to be present whenever there are three ordinary single bonds from a carbon atom to *any* other three atoms, provided that there is an opportunity for conjugation with another multiple bond.

In addition to the above-mentioned *first-order hyperconjugation*, a weaker type of hyperconjugation, *second-order hyperconjugation*, is also assumed to occur whenever two quasi-multiple bonds are conjugated, as, for example, in ethane:

$$H_3{\equiv}C{-}C{\equiv}H_3$$
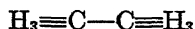
This type of hyperconjugation, however, presumably functions in all but the simplest molecules, and its effects therefore cannot be evaluated separately (44, 48). The term *hyperconjugation* is usually restricted to first-order hyperconjugation.

While each of the above methods of presentation of first-order hyperconjugation differs in terminology and in specific detail, it should be noted that in es-

---

[2] Contributions from structures such as

$$H^- \quad CH_2{=}C{-}\overset{+}{C}{-}$$
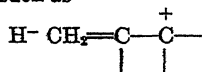
are, of course, also possible, but these are generally neglected as being of less importance (45, 46).

sentials the same concept is involved: the tendency of the electrons to concentrate in the direction of the unsaturated atom in a system which contains a saturated atom joined to an unsaturated atom of identical nuclear charge (25).

III. APPLICATIONS OF THE CONCEPT OF HYPERCONJUGATION

The concept of hyperconjugation has been used to explain and to correlate phenomena in two fairly distinct fields—physical-organic and organic chemistry.

A. Applications in physical-organic chemistry

- (1) Bond lengths: From electron-diffraction studies of methylacetylene, dimethylacetylene, dimethyldiacetylene, diacetylene, cyanogen, and methyl cyanide, it has been found that t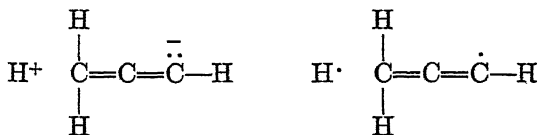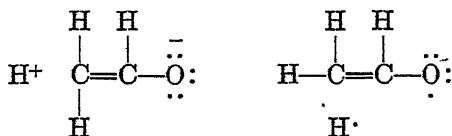he length of the carbon–carbon single bond adjacent to the carbon–carbon triple bond is approximately 0.08 Å. less than the normal carbon–carbon single bond length of 1.54 Å. (38). For methylacetylene this shortened bond length has been confirmed spectroscopically (1, 23). The decrease in length of the carbon–carbon bond has been attributed (38) to the partial double-bond character of the bond, which is due in the main to hyperconjugation resulting from contributions to the normal state of structures such as:

$$
\begin{array}{ccc}
 & \text{H} & & \text{H} \\
 & | & & | \\
\text{H}^+ & \text{C}{=}\text{C}{=}\overset{..}{\overset{-}{\text{C}}}{-}\text{H} & \qquad \text{H} \cdot & \text{C}{=}\text{C}{=}\overset{\cdot}{\text{C}}{-}\text{H} \\
 & | & & | \\
 & \text{H} & & \text{H}
\end{array}
$$

The bond length of a carbon–carbon single bond adjacent to a carbon–carbon double bond has been found by electron-diffraction studies to be normal to within the experimental error in "isobutene" (2-methylpropene), tetramethylethylene, mesitylene, and hexamethylbenzene (37). This is not unexpected. Since, owing to steric effects, a double bond can conjugate with only one carbon–hydrogen bond of a methyl group rather than with all three, the calculated decrease in length of the carbon–carbon single bond is only 0.03 Å., a value which is close to the limit of experimental error in electron-diffraction methods (38).

The carbon–carbon distance in acetaldehyde has been found to be approximately 0.04 Å. less than the normal value (42). This shortening has likewise been attributed partly to hyperconjugation, resulting from resonance with structures such as[3]:

$$
\begin{array}{ccc}
 & \text{H} \quad \text{H} & & \text{H} \quad \text{H} \\
 & | \quad\ | & & | \quad\ | \\
\text{H}^+ & \text{C}{=}\text{C}{-}\overset{..}{\overset{-}{\text{O}}}: & \qquad \text{H}{-} & \text{C}{=}\text{C}{-}\overset{..}{\overset{\cdot}{\text{O}}}: \\
 & | & & \\
 & \text{H} & & \text{H}\cdot
\end{array}
$$

[3] The structures given in reference 42 obviously contain typographical errors and have therefore been corrected here.

and partly to a formal charge effect resulting from resonance with the structure:

$$H_3C \overset{\overset{\displaystyle H}{|}}{\underset{+}{C}} \overset{\cdot\cdot}{\underset{\cdot\cdot}{O}}:$$
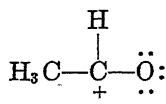
(2) *Dipole moments:* The large increase in dipole moment of methylchloroform as compared with chloroform was attributed by Maryott, Hobbs, and Gross (32) to a transfer of charge from the methyl carbon atom to the adjacent carbon atom and the transfer in turn of some of this charge to the chlorine atom. This is essentially a second-order hyperconjugation effect, but it was first discussed from this point of view by Hurdis and Smyth (27). They pointed out that three resonance structures of the type

$$H^+ \quad :\overset{\overset{\displaystyle Cl}{|}}{\underset{|}{C}} \quad Cl^-$$
$$Cl$$
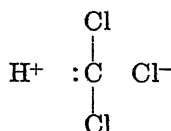
can make small contributions to the structure of chloroform. Some support for such a formulation comes from the apparent ability of the hydrogen to form hydrogen bonds, and also from the fact that the hydrogen is bound slightly more tightly to the carbon in chloroform than to the carbon in methyl chloride, as evidenced by Raman spectra (24). For methylchloroform nine resonance structures of the type

$$H^+ \quad \overset{\overset{\displaystyle H \quad Cl}{||}}{\underset{\underset{\displaystyle H \quad Cl}{||}}{C=C}} \quad Cl^-$$
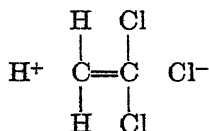
can be written. The contributions of these additional structures are postulated to account for the observed large increase in moment. Similar considerations account for the somewhat smaller increase in moment of 2,2-dichloropropane as compared with 1,1-dichloroethane.

The moment of 1-chloro-1-nitroethane has been found to be 0.22 D higher than the value expected on the basis of the moments of chloronitromethane and of the monosubstituted compounds; the corresponding propane compound has a moment 0.39 D higher than expected (27). These effects were attributed by Hurdis and Smyth to the fact that, in the case of chloronitromethane, only four structures of the following types, which would be expected to raise the moment, can be written:
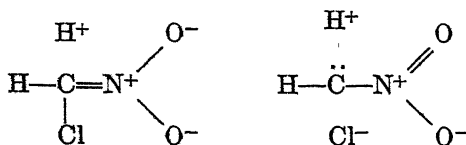
For 1-chloro-1-nitroethane, on the other hand, additional structures involving hyperconjugation, such as

$$
\begin{array}{ccc}
\underset{\underset{\underset{H}{|}}{\overset{H^+}{\underset{|}{C}}=\overset{H}{\underset{Cl}{C}}}{H}\!-\!\!\!\!\!\!\!\!\!\!\!\!\! & N & \begin{matrix} O \\ \diagup \\[-4pt] \diagdown \\ O^- \end{matrix}
\end{array}
$$
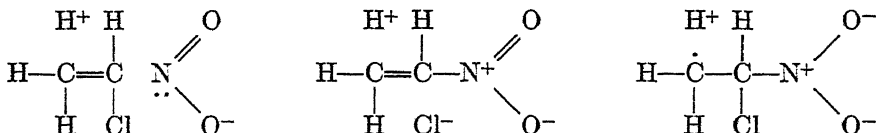
can be written; and the contributions of these structures were assumed to account for the observed increase in moment. Similar considerations can be applied to 1-chloro-1-nitropropane.

The moment of acetaldehyde has been found to be 0.45 D higher than that of formaldehyde. Hurdis and Smyth (28) attribute this increase in moment in acetaldehyde partly to the moment induced in the methyl group by the dipole of the carbon–oxygen bond and partly to hyperconjugation. In the case of formaldehyde, contributions of resonance structures of the following type would be expected to increase the moment:

Structures similar to these can be written for acetaldehyde, as well as three structures of the type:
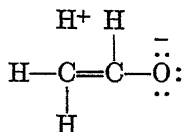
It will be recalled that results of electron-diffraction studies also indicate the influence of hyperconjugation in acetaldehyde (42).

The effect of hyperconjugation on the dipole moment is also shown by the large rise in moment of *trans*-crotonaldehyde as compared with acrolein (28). In addition to polar structures analogous to those which can be written for acrolein, such as
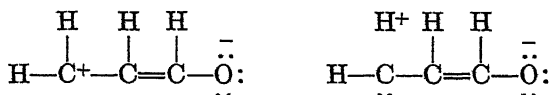
three further structures involving hyperconjugation are possible for *trans*-crotonaldehyde:
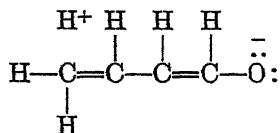
Similar considerations have been used to account for the moments of propylene, p-tolualdehyde, methyl cyanide, acrylonitrile, crotononitrile, and isocrotyl chloride (28).

The values of the dipole moments of toluene, ethylbenzene, isopropylbenzene, and tert-butylbenzene have been interpreted on the basis of the combined inductive and hyperconjugative effects (2, 7). The latter effect, however, seems to be of relatively minor importance in these compounds (2, 28, 45).

(3) Molecular refractivities: Mulliken (35) has attributed to hyperconjugation the increase in the exaltation of refractivity in methyl-substituted benzenes with increase in the number of methyl groups substituted. The lower refractivities of centrally substituted butadienes as compared with butadiene, and the increasingly large exaltations found with increasing end-substitution, are also postulated to be in part hyperconjugation effects.

(4) Absorption spectra: 1,3-Cyclopentadiene and 1,3-cyclohexadiene have their first absorption region at considerably longer wave lengths, and the bands are somewhat weaker than expected. These effects have been given a theoretical explanation on the basis of hyperconjugation by Mulliken (33, 34). The observed displacements of the spectra toward longer wave lengths when alkyl groups are substituted for hydrogen atoms in ethylene, butadiene, benzene, and other unsaturated compounds have similarly been attributed to hyperconjugation (34).

(5) Heats of hydrogenation: Conant and Kistiakowsky (15) found that the heat of hydrogenation of 1,3-cyclopentadiene is 50.9 kcal. per mole, as compared with 57.1 kcal. for 1,3-butadiene. Mulliken (34) noted that the data suggest an added effect of hyperconjugation in stabilizing 1,3-cyclopentadiene, as indicated in the following formula:

$$
\begin{array}{ccc}
HC & \!\!\!\!-\!\!\!\!-\!\!\!\! & CH \\
\| & & \| \\
HC & & CH \\
& \diagdown\ \diagup & \\
& C & \\
& \| & \\
& H_2 &
\end{array}
$$
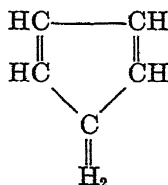
However, Mulliken considered that the low heat of hydrogenation of the compound may be due as much to the instability of the aliphatic five-membered ring as to the stability of the unsaturated compound. From the value 55.4 kcal. for 1,3-cyclohexadiene, where the aliphatic six-membered ring would be expected to have normal stability, it appears that hyperconjugation has a smaller, though appreciable, stabilizing effect.

The heats of hydrogenation of methylated ethylenes indicate an increased stability of the double bond with increase in the number of substituted methyl groups (15), an effect which might be attributed to hyperconjugation. The heats of bromination (16), however, show a trend opposite to that of the heats of hydrogenation, and Mulliken (34) has suggested that the heat effects may be due, in part at least, to causes other than hyperconjugation.

(6) Depolarization potentials: The depolarization potentials of a series of phenyl alkyl ketones (18) and of a series of p-alkylbenzaldehydes (5), as measured

polarographically, have been explained on the basis of the relative importance of the inductive and hyperconjugative effects of the alkyl groups.

(7) *Dissociation constants:* Baker, Dippy, and Page (6) have determined the thermodynamic dissociation constants for a series of *p*-alkyl-substituted benzoic acids. If hyperconjugation is of importance, a complete or partial inversion in the relative values of the dissociation constants anticipated on the basis of the inductive effect would be expected. Such an inversion was established experimentally, as it was found that the ethyl and isopropyl derivatives were stronger acids than the methyl and *tert*-butyl compounds. Baker, however, postulated that heat capacity and entropy effects might be at least partly responsible for the observed order.

Davies (17) determined the basic dissociation constants of a series of *p*-alkyl-dimethylanilines. Since the basic strengths were found to decrease in the sequence methyl > isopropyl > tertiary butyl, Davies postulated that the hyperconjugative effect predominated over the inductive effect.

(8) *Phosphorescence:* Lewis and Kasha (31) were able to obtain phosphorescence from diisopropyl ketone, but not from acetone. On the basis of their theory of phosphorescence, they attributed the effect to hyperconjugation in the diisopropyl compound, which allowed a wider separation of the odd electrons.

B. Applications in organic chemistry

The influence of hyperconjugation on the reactivity of organic compounds was first explicitly recognized by Baker and Nathan (3, 9, 10) as a result of the study of the reaction velocities of a series of *p*-alkylbenzyl bromides with pyridine. The velocity of formation of the quaternary salt was assumed to be facilitated by an increase in the ease of anionization of the bromine atom, due to the electron release of the alkyl group. Since the velocities decreased in the sequence methyl > ethyl > isopropyl > tertiary butyl, which is the reverse of the order expected on the basis of the inductive effect, Baker and Nathan postulated an additional effect due to hyperconjugation.

They assumed that the effect diminished with a decrease in the number of hydrogen atoms bonded to the α-carbon atom, becoming zero in the tertiary butyl group. They also emphasized the importance of the presence of a conjugated system; but they assumed that hyperconjugation could also function in those systems in which the displacement of the pair of electrons is rendered possible by the fission of a group with its bond electrons, as, for example:

$$H\text{---}CH_2\text{---}CH_2\text{---}X$$
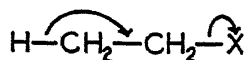
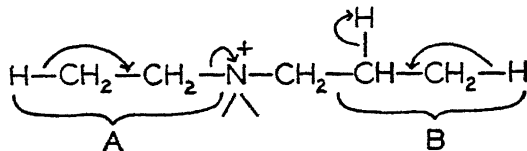If the completion of the system should require the separation as a negative ion of a group which normally ionizes as a positive ion, as, for example, hydrogen, they assumed that hyperconjugation could not occur.

With the aid of the concept of hyperconjugation, Baker and Nathan (10) also were able to explain the course of the following chemical reactions.

Ethylene, rather than higher olefins, is eliminated in the decomposition of

quaternary ammonium salts (22). Hyperconjugation, which can function as indicated at A, but cannot function at B because the elimination of a negative ion cannot occur, was assumed to be the decisive factor:
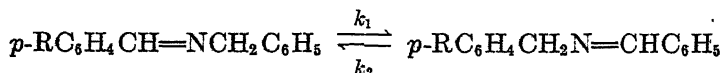
$$\text{H--CH}_2\text{--CH}_2\text{--}\overset{+}{\text{N}}\text{--CH}_2\text{--}\overset{\overset{\text{H}}{|}}{\text{CH}}\text{--CH}_2\text{--H}$$

$$\underset{\text{A}}{} \qquad\qquad\qquad \underset{\text{B}}{}$$

The substitution of p-alkyltoluenes by electrophilic reagents, which usually occurs ortho to the methyl group (12, 21), contrary to the known inductive effects, was explained by the greater capacity for electron release of the methyl group, due to hyperconjugation.

The lack of reactivity of isobutyl compounds in reactions of alkyl halides which involve the anionization of the halogen atom, as, for example, the reaction with sodium phenoxide (40), was also explained on the basis of the weak hyperconjugation of the isobutyl group. Similarly, the ionization of hydrogen from methyl and methylene groups in the Wagner–Meerwein reaction (4) was assumed to be a hyperconjugation effect, as indicated in the formula:

$$\text{H--CH}_2\text{--}\overset{\overset{\text{R}}{|}}{\underset{|}{\text{C}}}\text{--}\text{C--}\overset{..}{\text{Y}}$$
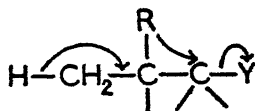
Baker and Nathan's original work had not given any indication as to whether hyperconjugation was a mesomeric or an electromeric effect, since the reaction studied was one facilitated by electron accession to the point of attack. It is known that a mesomeric effect is able to retard a reaction facilitated by electron recession from the point of attack, whereas an electromeric effect cannot retard such a reaction; therefore, Baker, Nathan, and Shoppee (11) studied the prototropic change in the azomethine system, which is known to be facilitated by electron recession fron the triad system (41):

$$p\text{-RC}_6\text{H}_4\text{CH}\!=\!\text{NCH}_2\text{C}_6\text{H}_5 \underset{k_2}{\overset{k_1}{\rightleftharpoons}} p\text{-RC}_6\text{H}_4\text{CH}_2\text{N}\!=\!\text{CHC}_6\text{H}_5$$

The velocity of interconversion of the system $(k_1 + k_2)$ was found to decrease in the order tertiary butyl > isopropyl > methyl; hence hyperconjugation is a mesomeric effect.

It was thought, however, that evidence from the previous kinetic studies was not completely free from the possibility of electromeric influence. Baker and Hemming (8), therefore, studied the influence of hyperconjugation on the following equilibrium, as the equilibrium state is known to be unaffected by polarizability effects:

$$p\text{-RC}_6\text{H}_4\text{CHO} + \text{HCN} \rightleftharpoons p\text{-RC}_6\text{H}_4\text{CH(OH)CN}$$
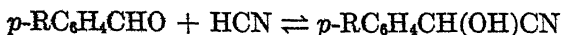
It was postulated that hyperconjugation would increase the stability of the free aldehyde to a greater extent than it would that of the cyanohydrin, because the conjugation can extend to the side-chain carbonyl in the aldehyde. If the hyperconjugative effect predominates over the inductive effect, the stabilities of the aldehydes relative to the cyanohydrins should decrease in the order: methyl > ethyl > isopropyl > tertiary butyl > hydrogen. This sequence was observed experimentally. Results of Lapworth and Manske (30) for a series of phenyl alkyl ketones were explained similarly.

The first completely satisfactory evidence for hyperconjugation from kinetic studies was not obtained until 1940. Hughes, Ingold, and Taher (26) pointed out that previous data had given either only incomplete inversion of series, or differences in reaction rates which were so small as to be difficult to interpret. They studied the effects of the alkyl groups on the rates of hydrolysis and alcoholysis of a series of p-alkylbenzylhydryl chlorides. On the basis of the inductive effect, the sequence of reaction velocities would be expected to be hydrogen < methyl < ethyl < isopropyl < tertiary butyl; but if hyperconjugation predominates, the sequence should be hydrogen < {methyl > ethyl > isopropyl > tertiary butyl}. The latter sequence was obtained for the hydrolysis. The quantitative data were unequivocal, as the rate range from hydrogen to methyl was 1:30, and the increase in rates throughout the series was regular. Robinson's suggestion (39) that actual ionization of the hydrogen of the methyl group might have occurred in the reaction was shown by deuterium-exchange experiments to be untenable.

Another application of the concept of hyperconjugation was made by Evans (20) to explain the results of his study of the rates of bromination of a series of phenyl n-alkyl ketones and of isobutyrophenone. He attributed to hyperconjugation the large increase in the activation energy in going from acetophenone to propiophenone, and the approximate constancy of the activation energies of propiophenone, butyrophenone, and valerophenone. However, the equivalence of the activation energies of propiophenone and isobutyrophenone could not be explained on this basis.

Hughes, Ingold, Masterman, and McNulty (25) have applied the Baker-Nathan effect in an explanation of the accelerating action of α-alphyl substituents on first-order and second-order elimination reactions. They emphasize, however, that they prefer to use the concept of hyperconjugation in its broader aspect, as a tendency of electrons to concentrate in the direction of unsaturated atoms. This latter view they use to account for the results of Linstead and Kon (29), which show that, in the tautomerism of unsaturated acids and ketones, the introduction of alkyl groups at either end of the three-carbon system shifts the equilibrium in such a direction as to place the unsaturation next to the alkyl group.

A further application of the concept of hyperconjugation was made by Davies (17), who studied the velocity of the reaction of p-alkyldimethylanilines with methyl iodide. The sequence obtained for the velocity constants (methyl > isopropyl > tertiary butyl) is not expected on the basis of the inductive effect,

and, since a steric effect cannot be present, Davies explained the results on the basis of hyperconjugation.

The fact that the rate of hydrolysis of potassium p-ethylphenylsulfate is greater than that of potassium p-tolylsulfate was interpreted by Burkhardt, Horrex, and Jenkins (14) as a hyperconjugation effect. They assumed that hyperconjugation also accounts for the rapidity of hydrolysis of o-isopropylphenylsulfate as compared with the o-ethyl compound, although steric factors are generally of predominant importance when the substituent is in the ortho position.

Davies and Hammick (19), in a study of the complexes of tetranitromethane and alkylbenzenes in carbon tetrachloride solution, found that the stability of the complexes increased from benzene through toluene and ethylbenzene, fell in isopropylbenzene, and then rose in the tertiary butyl compound. Since the stability of the complex presumably increases with an increase in the anionoid character of the aromatic nucleus, Davies and Hammick attributed to hyperconjugation the drop in stability from the ethyl to the isopropyl derivative.

Wheland has applied the concept of hyperconjugation in an explanation of the normal addition of acids to carbon–carbon double bonds (46), and also to account for meta substitution of toluene by free radicals (47).

REFERENCES

(1) BADGER AND BAUER: J. Chem. Phys. **5**, 599 (1937).
(2) BAKER: J. Chem. Soc. **1939**, 1150.
(3) BAKER: Trans. Faraday Soc. **37**, 632 (1941).
(4) BAKER: *Tautomerism*, pp. 299–304. George Routledge & Sons, London (1934).
(5) BAKER, DAVIES, AND HEMMING: J. Chem. Soc. **1940**, 692.
(6) BAKER, DIPPY, AND PAGE: J. Chem. Soc. **1937**, 1774.
(7) BAKER AND GROVES: J. Chem. Soc. **1939**, 1144.
(8) BAKER AND HEMMING: J. Chem. Soc. **1942**, 191.
(9) BAKER AND NATHAN: J. Chem. Soc. **1935**, 1840.
(10) BAKER AND NATHAN: J. Chem. Soc. **1935**, 1844.
(11) BAKER, NATHAN, AND SHOPPEE: J. Chem. Soc. **1935**, 1847.
(12) BRADY AND DAY: J. Chem. Soc. **1934**, 114.
(13) BURKHARDT AND EVANS: Mem. Proc. Manchester Lit. Phil. Soc. **77**, 37 (1933).
(14) BURKHARDT, HORREX, AND JENKINS: J. Chem. Soc. **1936**, 1654.
(15) CONANT AND KISTIAKOWSKY: Chem. Rev. **20**, 181 (1937).
(16) CONN, KISTIAKOWSKY, AND SMITH: J. Am. Chem. Soc. **60**, 2764 (1938).
(17) DAVIES: J. Chem. Soc. **1938**, 1865.
(18) DAVIES AND EVANS: J. Chem. Soc. **1939**, 546.
(19) DAVIES AND HAMMICK: J. Chem. Soc. **1938**, 763.
(20) EVANS: J. Chem. Soc. **1936**, 785.
(21) GANGULY AND LEFEVRE: J. Chem. Soc. **1934**, 1697.
(22) HANHART AND INGOLD: J. Chem. Soc. **1927**, 997.
(23) HERZBERG, PATAT, AND VERLEGER: J. Phys. Chem. **41**, 123 (1937).
(24) HIBBIN: Chem. Rev. **18**, 14 (1936).
(25) HUGHES, INGOLD, MASTERMAN, AND McNULTY: J. Chem. Soc. **1940**, 899.
(26) HUGHES, INGOLD, AND TAHER: J. Chem. Soc. **1940**, 949.
(27) HURDIS AND SMYTH: J. Am. Chem. Soc. **64**, 2829 (1942).
(28) HURDIS AND SMYTH: J. Am. Chem. Soc. **65**, 89 (1943).
(29) INGOLD: Ann. Reports Chem. Soc. **24**, 111 (1927).
(30) LAPWORTH AND MANSKE: J. Chem. Soc. **1930**, 1976.

(31) LEWIS AND KASHA: J. Am. Chem. Soc. **66,** 2100 (1944).

(32) MARYOTT, HOBBS, AND GROSS: J. Am. Chem. Soc. **63,** 659 (1941).

(33) MULLIKEN: J. Chem. Phys. **7,** 121 (1939).

(34) MULLIKEN: J. Chem. Phys. **7,** 339 (1939).

(35) MULLIKEN: J. Chem. Phys. **7,** 356 (1939).

(36) MULLIKEN, RIEKE, AND BROWN: J. Am. Chem. Soc. **63,** 41 (1941).

(37) PAULING AND BROCKWAY: J. Am. Chem. Soc. **59,** 1223 (1937).

(38) PAULING, SPRINGALL, AND PALMER: J. Am. Chem. Soc. **61,** 927 (1939).

(39) ROBINSON: Chemistry & Industry **55,** 962 (1936).

(40) SEGALLER: J. Chem. Soc. **1913,** 1421

(41) SHOPPEE: J. Chem. Soc. **1933,** 1117.

(42) STEVENSON, BURNHAM, AND SCHOMAKER: J. Am. Chem. Soc. **61,** 2922 (1939).

(43) WHELAND: J. Chem. Phys. **2,** 474 (1934).

(44) WHELAND: *The Theory of Resonance and its Applications to Organic Chemistry,* p. 87. John Wiley and Sons, Inc., New York (1944).

(45) Reference 44, pp. 133–4.

(46) Reference 44, pp. 235.

(47) Reference 44, pp. 263–4.

(48) WHELAND AND PINKSTON: J. Chem. Phys. **12,** 69 (1944).

THE REACTIONS OF NITROGEN TETROXIDE WITH ORGANIC COMPOUNDS

J. L. RIEBSOMER

Department of Chemistry, De Pauw University, Greencastle, Indiana

CONTENTS

I. INTRODUCTION

While certain reactions of nitrogen tetroxide with organic compounds were studied more than seventy-five years ago, no one has ever published a comprehensive review of this field. The variety of reactions which nitrogen tetroxide exhibits and the fact that in recent years it has become readily available at low cost make such a review seem very desirable.

The difficulties besetting this literature search and the interpretation of the experimental work should be stated at the outset. In much of the earlier work the authors allowed "nitrous fumes" (which generally referred to nitrogen trioxide) to react with organic compounds. These "nitrous fumes" were usually generated from arsenious oxide and nitric acid of various concentrations. Obviously, this reagent consisted not only of nitrogen trioxide but also of the

equilibrium mixture of nitric oxide and nitrogen tetroxide. Since it has been demonstrated by Lunge (108) that the composition of "nitrous fumes" varies, depending upon the concentration of the nitric acid, it is obvious that the research done with this reagent is subject to criticism because one of the reactants was probably of unknown composition. While it may be assumed in some instances that the nitrogen tetroxide reacts independently of the nitric oxide, such is not necessarily the case. In some cases "nitrous fumes" give substantially the same products as pure nitrogen tetroxide. Accordingly, it was considered necessary to include for this study reactions in which "nitrous fumes" or nitrogen trioxide were used.

Studies involving the reaction of organic compounds with nitric oxide or nitrogen pentoxide, where these were the only oxides used, have been purposely omitted.

Many interesting investigations have been carried out by allowing organic compounds to react with either organic or inorganic nitrites in aqueous solutions of acids such as hydrochloric acid. The first step in most of these reactions is the formation of nitrous acid, which may in turn form oxides of nitrogen as well as nitric acid. Since these studies would lead to the consideration of diazotizations as well as other transformations, they have been considered outside the scope of this review. Most reactions of oxides of nitrogen in aqueous solutions have not been given consideration, because in such cases one is dealing with mixtures of nitric and nitrous acids.

Unfortunately, in many of the investigations the authors were not always clear as to whether the oxides of nitrogen and the solvents were dried before use. In much of the work yields of the products formed and the conditions of the experiments were not stated. It is reasonable to assume that some of the yields were not published because they were embarrassingly low. In many cases the proof of the nature of the products formed rested only on an analysis, which often leaves much to be desired.

Finally, the experimental work and its interpretation are often very difficult because of the multiplicity of products and the formation of explosive, unstable, and inseparable oils. Regardless of whether one starts with pure dry reagents, there is always the probability (especially at higher temperatures) of the partial oxidation of the organic compound to form water, which in turn gives rise to more or less nitric and nitrous acids.

At best one is often dealing with a mixture of reactants. Accordingly, it is well to be charitable with any criticism concerning yields of products or interpretations offered in this area of research.

Because of the difficulties and uncertainties pointed out above, it is clear that much of the work already done needs repetition under conditions controlled as accurately as possible. In view of the availability of low-cost nitrogen tetroxide, some of these reactions should be of commercial value.

The reactions of nitrogen tetroxide may be classified under six main headings: (1) nitration, (2) oxidation, (3) reactions with compounds containing carbon–carbon multiple bonds, (4) reactions with alkali metal salts of organic acids, (5) reactions with organometallic compounds, (6) miscellaneous. In some instances

these reactions are difficult to classify because several types may take place simultaneously.

II: STRUCTURE AND PROPERTIES OF NITROGEN TETROXIDE

Nitrogen tetroxide has long been regarded as an equilibrium mixture, as indicated by the following equation:

$$N_2O_4 \rightleftharpoons 2NO_2$$

The dimolecular form is predominant at lower temperatures, but vapor-density measurements indicate complete conversion to the monomolecular form above 140°C. At 26.7°C. about 20 per cent of the tetroxide exists in the simpler form. In appearance nitrogen tetroxide varies from colorless crystals at −50°C. to black vapor at 183°C.; near room temperature the mixture is brown. The color changes are assumed to be related to the state of the equilibrium. It is believed that above 140°C. nitrogen tetroxide decomposes to form nitric oxide and oxygen, a change which is complete at 619.5°C. (117).

The boiling point of nitrogen tetroxide is reported variously from 20°C. to 69°C. (10). *International Critical Tables* gives 21.3°C. at 760 mm. The boiling point of 69°C. was reported for the substance after it had stood for one year in a sealed tube with phosphorus pentoxide. The high boiling point observed after intensive drying may indicate a change in molecular state. The melting point of nitrogen tetroxide is −11.5°C.

As would be expected nitrogen tetroxide is toxic, since it reacts with water to give nitric acid (98). Animals exposed to a concentration of one part per thousand die in a few minutes. Concentrations greater than five parts per million are harmful (103).

Nitrogen dioxide is an odd molecule and is paramagnetic (130a). Infrared studies indicate that the molecule is triangular in shape.
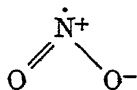
The structure of nitrogen tetroxide has not been clearly established (117). The three arrangements given in the older literature are shown by formulas I, II, and III. The modern counterparts of I and II are shown by formulas Ia and IIa (88a).
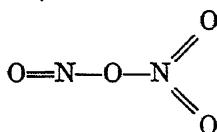
X-ray analysis of solid nitrogen tetroxide gives evidence for structure IIa. However, the N—N bond is weak, as indicated by the very small free-energy change of 1.2 Calories per mole for the dimerization of nitrogen dioxide (130a). The N—N bond is also abnormally long, 1.6 to 1.7 Å., whereas the usual single-bond N—N distance is about 1.4 Å.

Chemical evidence bearing on the above structures rather favors formula I (or Ia). Houston and Johnson (91) have assembled a series of arguments in favor of formula I. They point out that this formula shows nitrogen with valences of three and five, in accord wit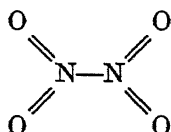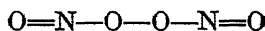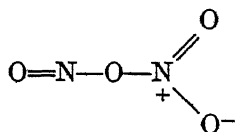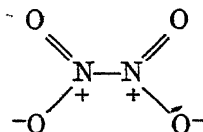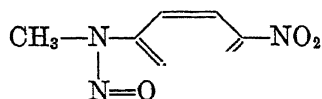h its reaction with water to produce both nitric and nitrous acids. Formulas II and III show nitrogen with a valence of five or three, respectively. The presence of a nitroso group is inferred from the reaction of methylphenylamine to form N-methyl-N-nitroso-p-nitroaniline (211):

$$CH_3—N—\langle\rangle—NO_2$$
$$\underset{N\!\!=\!\!O}{\big|}$$

The reaction with malonic ester to produce as the first step both nitro- and iso-nitroso-malonic esters (25) would follow from formula I. Alkyl halides were reported by Henry (90) to form alkyl nitrates, a fact which also would be in accord with formula I. Finally, the observation by Bamberger (11) that di-phenylmercury gave nitrosobenzene and mercury phenyl nitrate would clearly suggest that both nitroso and nitrate groups were present in the original molecule.

The arguments in favor of formulas II and III are generally less weighty. Meyer (119) concluded that formula III was correct on the basis of the reduction of the addition product of nitrogen tetroxide with amylene. This reduction gave no diamine; Meyer took this as evidence that the compound was $C_5H_{11}(ONO)_2$ and that it contained no carbon–nitrogen linkage. His dinitrite formula was later shown to be incorrect (121).

Nitrations with nitrogen tetroxide and possibly its thermal decomposition into nitric oxide and oxygen may be explained by formula II.

Schaarschmidt (171) suggested that nitrogen tetroxide might be considered an equilibrium mixture of I, II, and III.

III. NITRATION WITH NITROGEN TETROXIDE AND NITROGEN TRIOXIDE
(SEE TABLE 1)

A. Aromatic hydrocarbons

In general it seems safe to say that for the majority of nitrations nitrogen tetroxide offers no advantage over the classical methods using nitric and sulfuric acid mixtures. It has the disadvantage of being gaseous and accordingly more difficult to handle. In the preparation of certain specific isomers it may have an advantage.

As might be expected, the reaction of benzene with nitrogen tetroxide has probably been studied more than that of any other single aromatic compound and under a greater variety of conditions. The results have been variable.

As early as 1880, Leeds (100, 101) treated benzene with nitrogen trioxide at a low temperature for several days and reported the formation of nitrobenzene, oxalic acid, and picric acid. Yields were not stated. Apparently most of the benzene was recovered unchanged. The products formed with the reagents at the boiling point of benzene were not clearly established. Friedburg (63, 64) modified Leeds's experiment by first dissolving the nitrogen trioxide in carbon disulfide and then mixing this solution with benzene; he obtained a mixture of nitrobenzene and *p*-dinitrobenzene.

Wieland (244) allowed dry benzene and nitrogen tetroxide to react in a sealed tube at 80°C. for 6 hr. and obtained a low yield of nitrobenzene, 1,3,5-trinitrobenzene, picric acid, oxalic acid, and unidentified products. When these same reagents were allowed to stand 35 days at room temperature, more than 30 per cent of the benzene was converted to nitrobenzene (175) and unidentified products were formed. When Bass and Johnson (15) sealed dry benzene and nitrogen tetroxide in a tube and stored the mixture in the dark for three months, a trace of nitrobenzene was formed and most of the benzene was recovered. The same experiment carried out in sunlight resulted in an increased yield of nitrobenzene, accompanied by the formation of some *m*-dinitrobenzene and a 60 per cent recovery of the benzene.
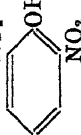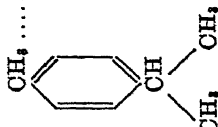
More promising results were obtained by Shorygin and Topchiev (200, 203), who produced yields of nitrobenzene as high as 65 per cent by allowing benzene and nitrogen tetroxide to react in the vapor phase diluted with an inert gas such as carbon dioxide or nitrogen. McKee and Wilhelm (109) produced nitrobenzene in yields as high as 36 per cent by passing benzene and nitrogen tetroxide over silica gel at 300–330°C. Activated alumina, pumice, titanium dioxide, or dehydrated bauxite substituted for the silica gel was ineffective as catalyst. German patent 207,170 (69) claimed that zinc oxide and cupric oxide (and other weakly basic metallic oxides) are effective in catalyzing the vapor-phase nitration of aromatic compounds with oxides of nitrogen (69). Anhydrous aluminum chloride and ferric chloride are also believed to catalyze the reaction of benzene with nitrogen tetroxide (21, 171, 215). When benzene and nitrogen tetroxide were allowed to stand at low temperature in the presence of mercury, dinitrophenol (isomer unstated) was formed (70).

Another interesting variation has been to mix benzene with 90–95 per cent sulfuric acid and then introduce nitrogen tetroxide at relatively low temperatures (17, 131, 149). By means of this procedure yields of nitrobenzene as high as 98 per cent have been obtained (218). Obviously, this method approaches the usual nitric–sulfuric acid nitration method, but the idea might be useful.

When benzene and nitrogen tetroxide were subjected to a glow discharge in a Siemens type of tube, nitrobenzene, *m*-dinitrobenzene, and trinitrophenol were formed (8).

The reactions of nitrogen tetroxide with toluene do not present as clear a picture as those with benzene because of the mixtures of isomers which may form. These reactions are further complicated because under some conditions oxidation

TABLE 1
Nitration

COMPOUND NITRATED	OXIDE OF NITROGEN	PRODUCTS FORMED	REFERENCE
C₆H₆	N₂O₄	C₆H₅NO₂, m-C₆H₄(NO₂)₂, O₂N—[ring with NO₂, OH, NO₂]—OH, p-C₆H₄(NO₂)₂, 1,3,5-C₆H₃(NO₂)₃	(15, 17, 21, 63, 64, 109, 131, 149, 175, 200, 203, 215, 218, 244)
C₆H₆	N₂O₃	C₆H₅NO₂, oxalic acid, picric acid	(100, 101)
C₆H₅CH₃	N₂O₄	o-NO₂C₆H₄CH₃, C₆H₅CH₂NO₂, C₆H₅CH(NO₂)₂, p-NO₂C₆H₄CH₃, C₆H₅CH₂NO, (COOH)₂, C₆H₅COOH, C₆H₅OH, C₆H₅CHO, C₆H₅CH₂NO₂	(17, 131, 175, 200, 201, 215, 216, 217, 218)
[isopropylbenzene structure: C₆H₅CH(CH₃)₂]	N₂O₃	NO₂ CH₃ CH—C— ONO₂ NO₂ CH—C—CH C=NO—C—CH₃ (O) NO₂ CH(CH₃)₂ NO₂	(147)
Naphthalene	N₂O₄	1-Nitronaphthalene, 1,5-dinitronaphthalene, 1,8-dinitronaphthalene	(131, 203)
Anthracene	N₂O₄	9,10-Dinitro-9,10-dihydroanthracene (heated with pyridine gave 9-nitroanthracene) 9,10-Dinitroanthracene, 9-nitroanthracene	(14, 116) (203)
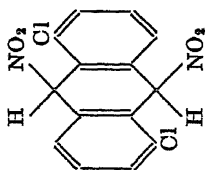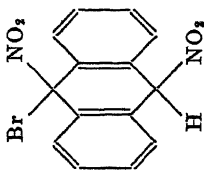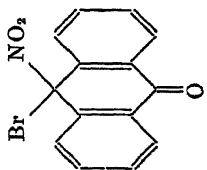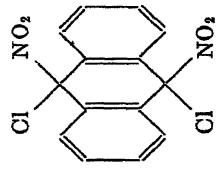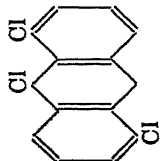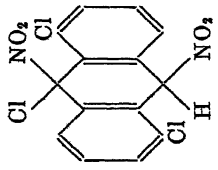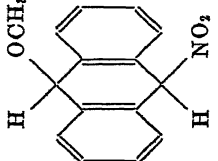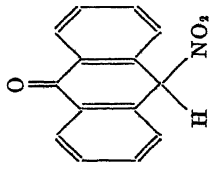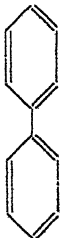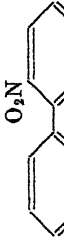
)-Phenylanthracene	N_2O_4	10-Nitro-9-phenylanthracene	(14)
)-Nitroanthracene	N_2O_4	Intermediate (heated with pyridine gave 9,10-dinitroanthracene)	(14)
l-Chloroanthracene	N_2O_4	Intermediate (heated with pyridine gave 1-chloro-9(or 10)-dinitroanthracene)	(14)
l,5-Dichloroanthracene	N_2O_4	(structure: H NO₂ / Cl ... Cl / H NO₂)	(14)
l,8-Dichloroanthracene	N_2O_4	Intermediate (heated with pyridine gave 1,8-dichloro-9(or 10)-nitroanthracene)	(14)
)-Bromoanthracene	N_2O_4	(structure: Br NO₂ / H NO₂)	(14)
),10-Dibromoanthracene	N_2O_4	(structure: Br NO₂ / O)	(14)

TABLE 1—*Continued*

COMPOUND NITRATED	OXIDE OF NITROGEN	PRODUCTS FORMED	REFERENCE
9,10-Dichloroanthracene	N_2O_4		(14)
	N_2O_4		(14)
	N_2O_3		(116)
	N_2O_3 or N_2O_4		(63, 64, 127, 203)
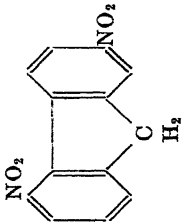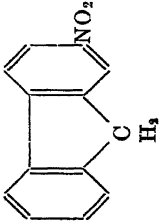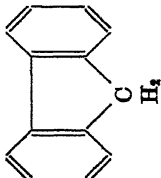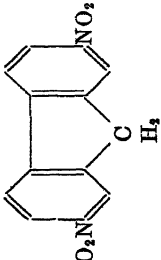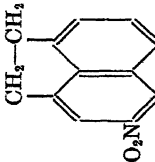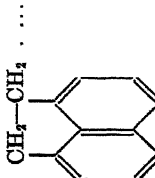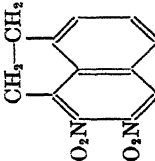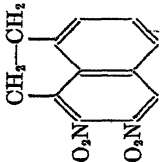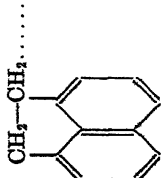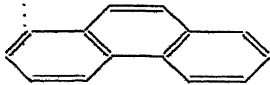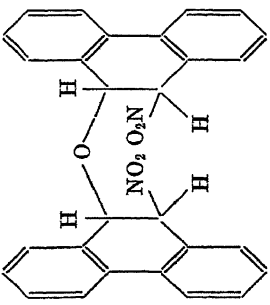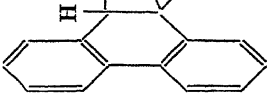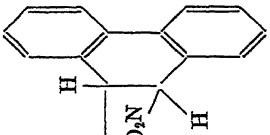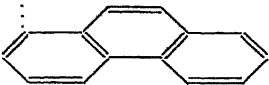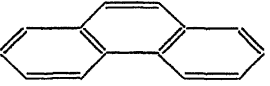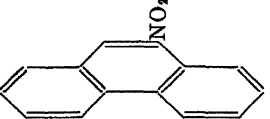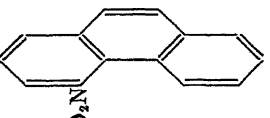
(127)

(127)

(127)

NO_2

C
H_2

NO_2

NO_2

NO_2

C
H_2

CH_2—CH_2

O_2N

O_2N

NO_2

NO_2

C
H_2

O_2N

CH_2—CH_2

CH_2—CH_2

O_2N

O_2N

O_2N

N_2O_3
or
N_2O_4

N_2O_3

N_2O_4

C
H_2

CH_2—CH_2

CH_2—CH_2

TABLE 1—Continued

COMPOUND NITRATED	OXIDE OF NITROGEN	PRODUCTS FORMED	REFERENCE
(phenanthrene)	N_2O_3	(structures)	(181)
(phenanthrene)	N_2O_4	(structures)	(203)
C_6H_5F	N_2O_4	$p\text{-}FC_6H_4NO_2$, $o\text{-}FC_6H_4NO_2$	(172, 173)
C_6H_5Cl	N_2O_4	$p\text{-}NO_2C_6H_4Cl$ and isomers	(17, 170, 172, 173, 215, 218)
C_6H_5Br	N_2O_4	$p\text{-}BrC_6H_4NO_2$, $o\text{-}BrC_6H_4NO_2$	(172, 173)
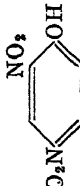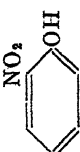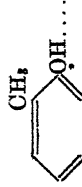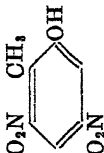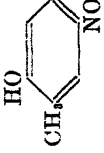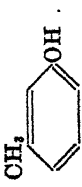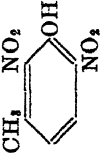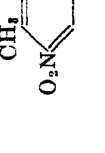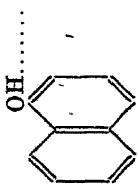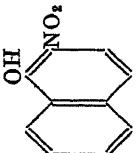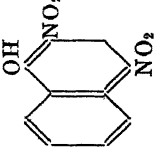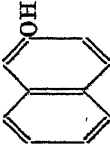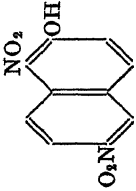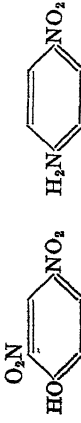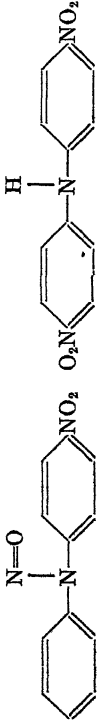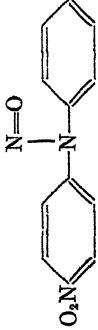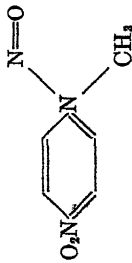
Reactant	Reagent	Products	References
C_6H_5I	N_2O_4	$p\text{-}IC_6H_4NO_2$, $o\text{-}IC_6H_4NO_2$	(172, 173)
$p\text{-}ClC_6H_4NO_2$	N_2O_4	$1,2,3,5\text{-}C_6H_2Cl(NO_2)_3$	(215)
C_6H_5OH	N_2O_3	$p\text{-}NO_2C_6H_4OH$, $o\text{-}NO_2C_6H_4OH$, $2,4\text{-}C_6H_3OH(NO_2)_2$, $2,4,6\text{-}C_6H_2OH(NO_2)_3$	(63, 64, 102, 203)
C_6H_5OH	N_2O_4	(nitrophenol structures)	(148, 244)
C_6H_5ONa	N_2O_4	$o\text{-}HOC_6H_4NO_2$, $p\text{-}HOC_6H_4NO_2$	(177)
(cresol)	N_2O_4	(nitrocresol structures)	(148, 244)
(phenol)	N_2O_4	(nitrophenol structures)	(148, 203)
(cresol)	N_2O_4	(nitrocresol structures)	(244)
(naphthol)	N_2O_4	(nitronaphthol structures)	(244)

TABLE 1—Continued

COMPOUND NITRATED	OXIDE OF NITROGEN	PRODUCTS FORMED	REFERENCE
naphthol (OH)	N_2O_4	nitro-naphthol (NO_2, O_2N, OH)	(203)
$C_6H_5NH_2$	N_2O_4	HO, O_2N / H_2N, NO_2	(203)
NHCOCH₃	N_2O_4	O_2N—NHCOCH₃	(203)
$(C_6H_5)_2NH$	N_2O_3	$(p\text{-}NO_2C_6H_4)_2NH$, $(2,4\text{-}(NO_2)_2C_6H_3)_2NH$; nitroso diphenylnitramine ($N=O$, NO_2); H—N(O_2N)(NO_2)	(63, 64); (211)
$(C_6H_5)_2NH$	N_2O_4	nitroso-diphenylamine ($N=O$, O_2N); $N=O$ diphenyl	(244)
$C_6H_5NHCH_3$	N_2O_4	O_2N—N($N=O$)(CH₃)	(211)
$C_6H_5N(CH_3)_2$	N_2O_4	$p\text{-}O_2NC_6H_4N(CH_3)_2$	(173, 203)

Starting compound	Reagent	Product	Reference
CH_3, $NHCH_3$ (benzene)	.	CH_3, $N(NO)CH_3$, NO_2, O_2N	(211)
$NH_2 \cdot HCl$ (benzene)	N_2O_3	NO_2, OH, O_2N	(227)
O_2N, $NH_2 \cdot HCl$	N_2O_3	NO_2, OH, O_2N	(227)
Cl, $NH_2 \cdot HCl$	N_2O_3	NO_2, OH, O_2N, Cl	(227)
Br, $NH_2 \cdot HCl$	N_2O_3	NO_2, OH, O_2N, Br	(227)
Br, Br, $NH_2 \cdot HCl$	N_2O_3	Br, OH, O_2N, Br, O_2N	(227)
CH_3, $NH_2 \cdot HCl$	N_2O_3	CH_3, OH, O_2N	(227)
CH_3, $NH_2 \cdot HCl$, Br	N_2O_3	O_2N, CH_3, OH, Br	(227)

TABLE 1—*Continued*

COMPOUND NITRATED	OXIDE OF NITROGEN	PRODUCTS FORMED	REFERENCE
CH_3-C_6H_4-$NH_2\cdot HCl$	N_2O_3	CH_3-$C_6H_2(OH)(NO_2)_2$	(227)
$NH_2\cdot HCl$ / $COOH$ benzene	N_2O_3	O_2N, OH, $COOH$ benzene	(227)
$HCl\cdot H_2N$-C_6H_4-$COOH$	N_2O_3	HO-$C_6H_2(COOH)(O_2N)$	(227)
naphthalene-$NH_2\cdot HCl$	N_2O_3	OH, NO_2 naphthalene	(227)
naphthalene-$NH_2\cdot HCl$	N_2O_4	NO_2, OH naphthalene	(227)
diphenyl ether (C_6H_5-O-C_6H_5)	N_2O_4	O_2N-C_6H_4-O-C_6H_4-NO_2 and NO_2-C_6H_4-O-$C_6H_4(NO_2)$	(158, 160)

Compound	Reagent	Product	Reference
C₆H₅—O—C₆H₅	N_2O_3	O_2N—C₆H₄—O—C₆H₅	(160)
—OCH₂	N_2O_4	—OCH₂—...—NO₂	(163)
—OCH₂CH₂O—	N_2O_4	O_2N—...—OCH₂—...—NO₂	(165)
Naphthalene—OC₂H₅	N_2O_3 or N_2O_4	O_2N—...—OCH₂CH₂O—...—NO₂	(164)
Naphthalene, NO₂ / OC₂H₅	N_2O_4	Naphthalene, NO₂ / OC₂H₅ / NO₂	(164)
$(CH_3)_2CHCH_2CH_2OC_6H_5$	N_2O_4	Product which on reduction gave $(CH_3)_2CHCH_2CH_2OC_6H_4NH_2$-$p$	(53, 54)
$C_6H_5NO_2$	N_2O_4	$C_6H_4(NO_2)_2$	(215)
p-$CH_3C_6H_4NO_2$	N_2O_4	O_2N—C₆H₂(CH₃)(NO₂)(NO₂)	(215)
Pyridine	N_2O_4	3-Nitropyridine	(202)

COMPOUND NITRATED	OXIDE OF NITROGEN	PRODUCTS FORMED	REFERENCE
Quinoline	N_2O_4	7-Nitroquinoline, 5,7-dinitroquinoline	(202)
Cyclohexane	N_2O_4	Nitrocyclohexane	(200)
	N_2O_3		(211)
p-CH$_3$C$_6$H$_4$NHSO$_2$C$_6$H$_4$CH$_3$	N_2O_4	4,2-CH$_3$(NO$_2$)C$_6$H$_3$NHSO$_2$C$_6$H$_4$CH$_3$ 4,2,6-CH$_3$(NO$_2$)$_2$C$_6$H$_2$NHSO$_2$C$_6$H$_4$CH$_3$ 4,2,6-CH$_3$(NO$_2$)$_2$C$_6$H$_2$N(N=O)SO$_2$C$_6$H$_4$CH$_3$	(14)
	N_2O_4		(99)
(C$_6$H$_5$)$_2$N=O	N_2O_4	(p-O$_2$NC$_6$H$_4$)$_2$N=O	(252)
(C$_6$H$_5$)$_2$NOH	N_2O_4	(p-O$_2$NC$_6$H$_4$)$_2$N=O	(252)
(p-CH$_3$C$_6$H$_4$)$_2$NOH	N_2O_4		(252)
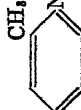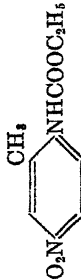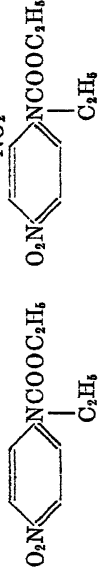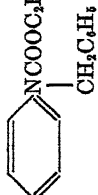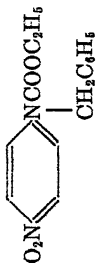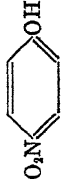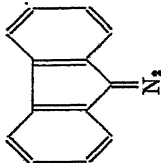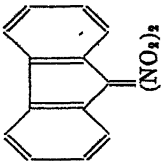
$CH_3C_6H_4NHCOOC_2H_5$	N_2O_4	CH_3-(ring)-$NHCOOC_2H_5$ with O_2N	(157, 161)
(ring)$NCOOC_2H_5$, C_2H_5	N_2O_4	O_2N-(ring)-$NCOOC_2H_5$, C_2H_5; NO_2, (ring)$NCOOC_2H_5$, C_2H_5, O_2N	(156)
$(C_6H_5)_2NCOOC_2H_5$	N_2O_4	$(p\text{-}O_2NC_6H_4)_2NCOOC_2H_5$	(159, 161)
(ring)$NCOOC_2H_5$, $CH_2C_6H_5$	N_2O_4	O_2N-(ring)-$NCOOC_2H_5$, $CH_2C_6H_5$	(167)
$(C_6H_5)_2C{=}C(C_6H_5)_2$	N_2O_4	C_6H_5, C_6H_5 $C{=}C$ $p\text{-}O_2NC_6H_4, C_6H_4NO_2\text{-}p$	(178)
$C_6H_5NHCONH_2$	N_2O_3 or N_2O_4	O_2N-(ring)-OH	(168)
$C_6H_5NHCNHC_6H_5$, $O{=}$	N_2O_3 or N_2O_4	O_2N-(ring)-$NHCNH$-(ring)-NO_2, $O{=}$; $C_6H_5N{=}C{-}NC_6H_5$, $N{=}O$, $N{=}O$	(168)

TABLE 1—Continued

COMPOUND NITRATED	OXIDE OF NITROGEN	PRODUCTS FORMED	REFERENCE
$(C_6H_5)_2NCNH_2$ (with C=O)	N_2O_3	$(p\text{-}O_2NC_6H_4)_2NCNHN{=}O$ (with C=O)	(168)
Structure: C_6H_5, C_2H_5 on $N{-}N{=}N{-}N$ backbone with C_6H_5, C_2H_5	N_2O_4	Structure: $p\text{-}NO_2C_6H_4$, $C_6H_4NO_2\text{-}p$, C_2H_5 on $N{-}N{=}N{-}N$ backbone with C_2H_5	(251)
Structure: C_6H_5, C_6H_5 on $N{-}N{=}N{-}N$ backbone with C_6H_5, C_6H_5	N_2O_4	Structure: $p\text{-}NO_2C_6H_4$, $C_6H_4NO_2\text{-}p$, C_6H_5 on $N{-}N{=}N{-}N$ backbone with C_6H_5	(251)
$N_2{=}CHCOOC_2H_5$	N_2O_4	$(NO_2)_2CHCOOC_2H_5$	(251)
$C_6H_5CCC_6H_5$ (with C=O and N_2)	N_2O_4	$C_6H_5CH(NO_2)_2$	(251)

N$_2$	N$_2$O$_4$	(NO$_2$)$_2$	(251)
CH$_4$	N$_2$O$_4$	CH$_3$NO$_2$	(221, 226)
CH$_3$CH$_2$CH$_3$	N$_2$O$_4$	CH$_3$NO$_2$, CH$_3$CH$_2$NO$_2$, CH$_3$CH$_2$CH$_2$NO$_2$, CH$_3$CH(NO$_2$)CH$_3$	(86, 87, 221, 226)
CH$_3$(CH$_2$)$_n$CH$_3$ (n = 3 to 7)	N$_2$O$_4$	CH$_3$(CH$_2$)$_n$CH$_2$NO$_2$, O$_2$NCH$_2$(CH$_2$)$_n$CH$_2$NO$_2$	(222, 223, 224, 225, 226)

of the side chain occurs. Leeds (102) allowed toluene to react with nitrogen trioxide and reported the formation of oxalic acid, benzoic acid, dihydroxybenzoic acid (orientation unstated), o-nitrotoluene, and a methyldinitrodihydroxybenzene. The conditions of the reaction were poorly defined, and the yields were not stated. Schaarschmidt and Smolla (175) mixed toluene with technical nitrogen tetroxide at room temperature and allowed these mixtures to stand for varying periods of time (32–108 days). They obtained yields of 19–35 per cent oxalic acid, 31–59 per cent benzoic acid, 0–0.5 per cent phenol, 0.5–21 per cent benzaldehyde, and 41–44 per cent nitrotoluenes. Bass and Johnson (15) observed no evidence of nitration when dry nitrogen tetroxide and toluene were sealed in a tube and allowed to stand. About 63 per cent of the toluene was recovered, and about a 25 per cent yield of benzoic acid was produced. No nitration was observed when the same mixture was sealed in a quartz tube and exposed to a quartz mercury arc at 55°C. for 4 hr.

When nitrogen tetroxide diluted with carbon dioxide was allowed to react with toluene for 2 hr. at 140–145°C., a 45 per cent conversion to nitrotoluenes was observed with the simultaneous formation of 4–8.3 per cent of nitrophenylmethane (α-nitrotoluene). The presence of ultraviolet light generally increased the yields (200). At 14°C. and without carbon dioxide as a diluent some nitrosophenylmethane was formed (201). Titov (216, 217) found a slight tendency for nitrogen tetroxide to cause nitration in the benzene ring but obtained mainly nitrophenylmethane, dinitrophenylmethane, and oxidation products, the latter being formed especially at higher temperatures (218).

When toluene was treated with nitrogen tetroxide in the presence of 90–94 per cent sulfuric acid, yields of mixed nitrotoluenes as high as 98 per cent were observed (17, 131, 218). Aluminum chloride also favored the formation of nitrotoluenes (215).

Xylene and mesitylene seemed to react with nitrogen tetroxide; evidently the products were a complex mixture (175). According to Leeds (102) xylene (isomer not stated) reacted with nitrogen trioxide to give oxalic acid, a nitroxylene, p-toluic acid, and phthalic acid.

p-Cymene reacted with nitrogen trioxide to produce p-toluic acid, oxalic acid, and a nitrocymene (100, 101, 102). However, Puranen (147) found that p-cymene reacted with nitrogen tetroxide in acetic acid solution to give a compound to which formula I was assigned.

I
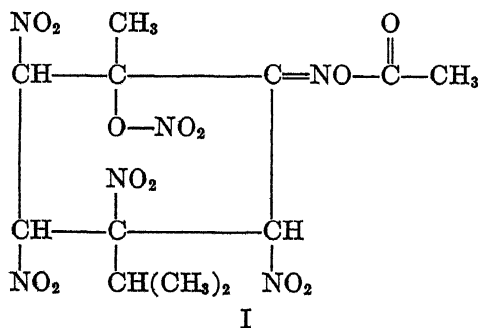
Naphthalene reacted with nitrogen trioxide to produce a mixture of nitronaphthalenes (100, 101). Shorygin and Topchiev (203) obtained a quantitative conversion of naphthalene to 1-nitronaphthalene by heating equimolar portions of naphthalene and nitrogen tetroxide at 150°C. Under other conditions various polynitro derivatives were formed. A high yield of 1-nitronaphthalene was also obtained by Pinck (131) by allowing the above substances to react in the presence of concentrated sulfuric acid.

Leeds (102) obtained a good yield of anthraquinone by adding nitrogen trioxide to anthracene in acetic acid. When no solvent was used, anthraquinone and an unidentified red oil were formed. Liebermann (106), using the same reagents, obtained 9-nitrosoanthrone and other products.

Anthracene and nitrogen tetroxide suspended in benzene reacted to give only a trace of anthraquinone (15). Anthracene in nitrobenzene was converted to anthraquinone in high yields (92). Meisenheimer and Connerade (116), as well as Barnett (14), carried out the same reaction in chloroform and obtained 9,10-dinitro-9,10-dihyrdoanthracene. Using the same reagents and solvent Shorygin and Topchiev (203) reported a 40 per cent yield of 9,10-dinitroanthracene along with 4–8 per cent of 9-nitroanthracene. It is not probable that both of these latter reports can be correct, since the conditions of the experiments seem to be substantially the same. The above examples, from which markedly different results were obtained depending on the solvent used, serve to illustrate the importance of the solvent in reactions involving nitrogen tetroxide.

Biphenyl was treated with nitrogen tetroxide under various conditions. When the reagents were mixed at room temperature 4-nitrobiphenyl and 2-nitrobiphenyl were produced (63, 64, 203). Monti et al. (127) reported an almost 100 per cent yield of 4-nitrobiphenyl when the reaction was carried out using "nitrous vapors" without a solvent. When acetic acid, ether, ligroin, or benzene was used as solvent at 0–25°C., no nitration took place. With acetic acid as solvent at 90–95°C., both 4,4'- and 2,4'-dinitrobiphenyl were formed.

When fluorene reacted in various solvents with "nitrous vapors" (127) near room temperature, 2-nitrofluorene was obtained in yields as high as 70 per cent. When the reaction was carried out in acetic acid at 90–95°C., a mixture of 2,5- and 2,7-dinitrofluorenes was formed; with pure nitrogen tetroxide only 2-nitrofluorene was reported.

Acenaphthene was nitrated with "nitrous fumes," using ether or petroleum ether as solvent; a 90–95 per cent yield of 5-nitroacenaphthene was formed. In benzene or acetic acid at 8–10°C., 5,6-dinitroacenaphthene was produced. When nitrogen tetroxide was used without a solvent, acenaphthene reacted very vigorously even at low temperatures, giving 5,6-dinitroacenaphthene (127).

When triphenylmethane was treated with "nitrous vapors" at room temperature in various solvents, triphenylcarbinol was formed (127). Neither diphenylmethane nor 1,2-diphenylethane reacted with "nitrous" fumes at 15–20°C.

Schmidt (181) allowed phenanthrene to react with nitrogen trioxide and obtained a small yield of products which he named bismononitrodihydrophenanthrene oxide (II) and bismononitrodihydrophenanthrene (III).
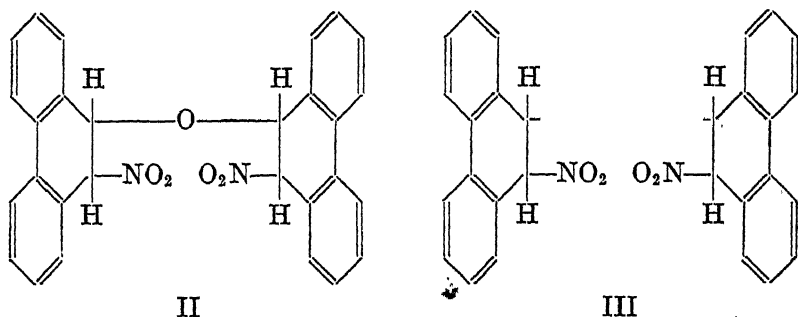
Nitrogen tetroxide and phenanthrene at 0°C. formed a mixture of isomers including the 2-nitro- (32 per cent), 9-nitro- (11 per cent), 4-nitro- (3 per cent), and a small amount of 3-nitro-phenanthrene (203)

B. Halogenated aromatic compounds

In general the simple halogenated aromatic compounds do not nitrate very efficiently with nitrogen tetroxide in the absence of concentrated sulfuric acid, aluminum chloride, or other catalytic agents (173). Fluorobenzene did not react with nitrogen tetroxide in carbon tetrachloride solution even after 72 hr. of contact. Iodobenzene under the same conditions was converted to the extent of 45 per cent to a mixture of o- and p-iodonitrobenzenes. Chloro- and bromobenzenes behaved similarly to iodobenzene with lower conversions. p-Chlorotoluene gave p-chlorobenzoic acid and unidentified nitration products (175). Purgotti (148) reported no nitration of bromobenzene, symmetrical tribromobenzene, 1,2,3,4-tetrabromobenzene, or hexabromobenzene by nitrogen tetroxide in various solvents. When chlorobenzene was nitrated in the presence of concentrated sulfuric acid, p-nitrochlorobenzene was the main product (17).

With aluminum chloride, ferric chloride, or phosphorus pentachloride as catalysts, nitrations of halogenated benzenes by means of nitrogen tetroxide have been more successful (170, 172, 173, 215). Titov (215) obtained a 96 per cent yield of the isomeric nitrochlorobenzenes from chlorobenzene. Comparable results have been obtained with fluoro-, bromo-, and iodo-benzenes. The p-nitro derivative was formed in the greatest proportion in all cases observed, usually to the extent of 90 per cent or more of the isomeric mixture. With homologues such as the chlorotoluenes, oxidation as well as nitration occurred. Schaarschmidt (170, 172) suggested that these reactions proceed with the intermediate formation of complexes of the type shown in formula IV:

$$2AlCl_3 \cdot 3(C_6H_5Cl : N_2O_4)$$

IV

These complexes decompose upon addition of water to give an unstable product (V), which then forms the nitro derivatives.

$$C_6H_5Cl : N_2O_4$$
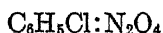
Barnett (14) treated various chloroanthracene derivatives with dry nitrogen tetroxide in carbon tetrachloride. 1-Chloroanthracene gave an addition compound which when heated with pyridine gave 1-chloro-9(or 10)-nitroanthracene. 1,5-Dichloroanthracene gave 1,5-dichloro-9,10-dinitro-9,10-dihydroanthracene, which upon heating with pyridine gave 1,5-dichloro-9-nitroanthracene. 9-Bromoanthracene gave 9-bromo-9,10-dinitro-9,10-dihydroanthracene, which upon heating with pyridine gave 9,10-dinitroanthracene. 9,10-Dichloro- and 9,10-dibromo-anthracenes gave unstable intermediate products which readily changed to produce anthraquinone.

C. Phenolic compounds

In the reaction of nitrogen trioxide with phenol Leeds (102) reported much carbonization with the formation of picric acid. The conditions of the experiment were not clearly defined. Nitrogen trioxide dissolved in carbon bisulfide reacted with phenol to give o- and p-nitrophenols and nitrosophenol (63, 64).

With nitrogen tetroxide phenol was readily nitrated, giving a mixture of the o- and p-nitro derivatives in good yields (60, 244). When chloroform or carbon tetrachloride was used as solvent, 2,4-dinitrophenol was the main product (148, 203). Anisole and phenetole under comparable conditions did not react.

Sodium phenoxide in carbon bisulfide reacted with nitrogen tetroxide to form a mixture of o- and p-nitrophenols (177) with the simultaneous formation of sodium nitrite.

Cresols when nitrated with nitrogen tetroxide generally formed polynitro derivatives (148, 203, 244). There is wide speculation as to which isomers are formed. The treatment of halogenated phenols with nitrogen tetroxide leads to ill-defined mixtures.

More promising results were reported by Shorygin and Topchiev (203) when 2-naphthol was allowed to react with nitrogen tetroxide in chloroform. About an 80 per cent yield of 1,6-dinitro-2-naphthol was formed.

D. Aromatic and aromatic-aliphatic amines

Vigorous reactions were observed by Leeds (102) when aniline, p-toluidine, and xylidine were brought in contact with nitrogen trioxide, but no definite products were obtained. Friedburg (63, 64) obtained 4-nitrodiphenylamine and 2,4-dinitrodiphenylamine by allowing diphenylamine to react with nitrogen trioxide in carbon disulfide solution.

According to Filippuichev and Petrov (57) and San Fourche and Bureau (169), primary aromatic amines are readily diazotized when treated with oxides of nitrogen (57). Varma and Krishnamurthy (227) allowed a series of aromatic amines (in the form of their hydrochlorides) to react with nitrogen trioxide; they generally obtained nitrophenols as products. In all instances reported the amino group was removed from the aromatic ring. For example, aniline hydrochloride was converted to 2,5-dinitrophenol; p-nitroaniline to 2,4-dinitrophenol; p-toluidine to 2,6-dinitro-p-cresol; o-aminobenzoic acid to 3-nitrosalicylic acid; and 1-aminonaphthalene to 2-nitro-1-naphthol.

Ryan and Egan (161) allowed diphenylamine to react with nitrous acid (presumably nitrogen trioxide) and obtained compound VI.

$$N\!=\!O$$
$$|$$
$$p\text{-}NO_2\,C_6H_4\!-\!N\!-\!C_6H_5$$
VI
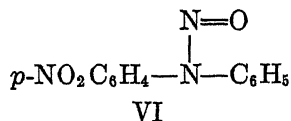
Similar results were obtained by Stoermer (211).

Stoermer (211) allowed a series of mixed aromatic-aliphatic amines to react with nitrogen trioxide or with nitrogen tetroxide in various solvents. In all instances reported the N-nitroso derivative was formed. In some instances nitration in the ring took place at the same time. As illustrations, methyl-m-tolylamine and nitrogen trioxide produced methyl-3,5-dinitrotolyl-N-nitroso-amine; ethyl-p-nitrophenylamine gave ethyl-p-nitrophenyl-N-nitrosoamine; and methyl-p-nitrophenylamine gave methyl-p-nitrophenyl-N-nitrosoamine.

Aniline reacted with nitrogen tetroxide in chloroform solution to give a 23 per cent yield of 2,4-dinitrophenol and a small quantity of p-nitroaniline (203). In benzene solution Witt (256) obtained a quantitative yield of benzenediazonium nitrate. Acetanilide under the same conditions produced 60 per cent of p-nitroacetanilide and 30 per cent of the ortho isomer, while N,N-dimethylaniline gave as high as 86 per cent of p-nitrodimethylaniline (173) and traces of the meta isomer.

Wieland (244) found that acetanilide and nitrogen tetroxide reacted in cold ether to form benzenediazonium nitrate and acetic acid and that p-dimethyl-aminoacetanilide gave no diazonium salt. Diphenylamine and nitrogen tetroxide reacted in cold ether to produce N-nitrosodiphenylamine, while in cold benzene or petroleum ether some N-nitrosodiphenylamine along with p-nitro-N-nitrosodiphenylamine was formed.

Ryan and Egan (161) reported an indefinite mixture of polynitro derivatives from the reaction between triphenylamine and nitrogen tetroxide.

p-Nitroaniline reacted with nitrogen tetroxide in benzene to give a mixture of 4,4'-dinitrodiazoaminobenzene and p-nitrobenzenediazonium nitrate. Either product could be formed in high yield depending on the conditions (91).

Battlegay and Kern (16) allowed p-toluenesulfonyl-p-toluidide to react with nitrogen tetroxide and obtained a mixture of p-toluenesulfonyl-2,4-dinitro-p-toluidide, p-toluenesulfonyl-p-2,6-dinitrotoluidide, and the N-nitroso derivative of the latter compound. Other p-toluenesulfonyl derivatives of highly substituted aromatic amines gave mainly the N-nitroso derivatives in high yields.

E. Aromatic ethers

In general the aromatic ethers which have been allowed to react with nitrogen tetroxide have produced a mixture of mono and (or) dinitro derivatives (14, 53, 54, 116, 158, 160, 161, 163, 164, 165). This type of reaction has been studied mainly by Ryan et al. Diphenyl ether gave 2,4'- and 4,4'-dinitrodiphenyl

ether and 2,4-dinitrophenol. 4-Nitrodiphenyl ether was formed when acetic acid was used as a solvent. Here, as in many other instances, the solvent has an important bearing on the course of the reaction. In some reactions considerable oxidation accompanied the nitration.

F. Miscellaneous aromatic and heterocyclic compounds

Salicylic acid reacted with nitrogen tetroxide to form 5-nitrosalicylic acid and picric acid (60). Nitrobenzene failed to undergo further nitration with nitrogen tetroxide even in the presence of aluminum chloride. Negative results were also obtained with benzoyl chloride and p-xylene, a result which is surprising, particularly for the latter compound (215).

With fuming sulfuric acid and nitrogen tetroxide at 5–7°C., nitrobenzene reacted to give dinitrobenzene (isomer not stated) in a 97.6 per cent yield. The same method with p-nitrotoluene gave a high yield of a mixture of 2,4-dinitro- and 2,4,6-trinitro-toluenes, while p-chloronitrobenzene gave a 98 per cent yield of trinitrochlorobenzene. p-Nitrotoluene reacted with fuming sulfuric acid, potassium persulfate, and nitrogen tetroxide to produce a 97.1 per cent yield of 2,4-dinitrotoluene.

Thiophene reacted with nitrogen tetroxide to give unidentified products (173). Schaarschmidt, Balzerkiewicz, and Gante (173) stated that pyridine did not undergo nitration, while Schorygin and Topchiev (202) found that when the reagents were diluted with carbon dioxide and heated in a sealed tube at 115–120°C. a 7–10 per cent yield of 3-nitropyridine was formed. The same authors observed no nitration of quinoline at room temperature and obtained less than 15 per cent of 7-nitroquinoline at 95–105°C. At 105–160°C. both 7-nitroquinoline and 5,7-dinitroquinoline were formed.

1,9-Benzanthrone reacted with dry nitrogen tetroxide without a solvent to produce a 96–98 per cent yield of 1-nitrobenzanthrone (99).

Di-p-tolylhydroxylamine produced o,o'-dinitrodi-p-tolylamine when it reacted with nitrogen tetroxide in cold ether or benzene solution (252). In the same publication Wieland reported that diphenylhydroxylamine reacted with nitrogen tetroxide to produce p,p'-dinitrodiphenylamine oxide and that diphenylamine oxide with nitrogen tetroxide also produced p,p'-dinitrodiphenylamine oxide.

Aryl urethans reacted with "nitrous fumes" to produce nitrourethans (156, 157, 159, 161, 167), along with smaller amounts of polynitro derivatives.

Tetraphenylethylene produced 1,2-diphenyl-1,2-di(p-nitrophenyl)ethylene when it reacted in chloroform solution with nitrogen tetroxide.

Various phenylureas were allowed to react with nitrogen trioxide or nitrogen tetroxide (168). For the most part nitro or polynitro derivatives were formed along with nitroso compounds. For example, symmetrical diphenylurea gave with nitrogen tetroxide sym-4,4'-dinitrodiphenylurea and sym-diphenyl-N,N'-dinitrosourea.

Ciusa and Pestalozza (28, 29, 30) added nitrogen tetroxide to ether solutions of

the phenylhydrazones of aromatic aldehydes. With benzaldehyde an almost quantitative yield of VII was formed, along with a little benzaldehyde and

$$NO_2$$

$$C_6H_5\overset{|}{C}\!\!=\!\!NNHC_6H_5$$

VII
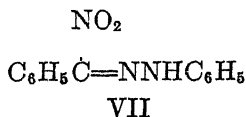
benzenediazonium nitrate, and oxidation products. The phenylhydrazones of other aromatic aldehydes behaved similarly.

Wieland and Reisenegger (251) allowed various diazo compounds and tetrazenes to react with nitrogen tetroxide in benzene solution. Ethyl diazoacetate produced a low yield of ethyl dinitroacetate; diazodesoxybenzoin gave dinitrophenylmethane; diazofluorene gave 9,9-dinitrofluorene; tetraphenyltetrazene gave *sym-p,p'*-dinitrotetraphenyltetrazene.

G. Aliphatic hydrocarbons

The nitroparaffins are most commonly prepared by the vapor-phase nitration with nitric acid of the lower molecular weight aliphatic hydrocarbons (86, 87, 88, 94). Up to the present better yields of the nitroparaffins are obtained with nitric acid than with nitrogen tetroxide.

A careful study was made by Hass, Dorsky, and Hodge (86) of the nitration of propane with nitrogen tetroxide. At 790–795°C. approximately equal quantities of nitromethane, nitroethane, 1-nitropropane, and 2-nitropropane were formed. Lower temperatures favored the formation of 2-nitropropane. In addition to the nitroparaffins mentioned, miscellaneous oxidation products including acids and aldehydes were formed. A large percentage of the starting materials did not react.

The only other work of significance in which nitrogen tetroxide was allowed to react with aliphatic hydrocarbons seems to be that of Urbánski and Sloń (221, 222, 223, 224, 225, 226). Nitration of propane at 100°C. gave 1-nitropropane, some dinitroparaffins, and oxidation products soluble in water. Nitration of methane at 200°C. gave nitromethane, polynitro derivatives, and oxidation products.

The hydrocarbons from *n*-pentane through *n*-nonane were nitrated with nitrogen tetroxide mostly at 200°C. They gave mixtures of mononitro derivatives, $CH_3(CH_2)_nNO_2$, and dinitro derivatives, $O_2NCH_2(CH_2)_nCH_2NO_2$, with conversions of 30 to 80 per cent depending upon the conditions. It would appear that the above-mentioned types of nitroparaffins would represent an oversimplification. On the basis of the work of Hass *et al.* one would expect a much greater variety of products. Perhaps it should be pointed out that this discussion of the work of Urbánski and Sloń has been based for the most part on abstracts. Accordingly, it may or may not represent a complete listing of the products found by these authors.

Shorygin and Topchiev (200) found that *n*-hexane produced a low yield of 2-nitrohexane when it reacted with nitrogen tetroxide diluted with carbon dioxide. The reaction was carried out for 1 hr. at 10–80°C. Application of the same pro-

cedure to cyclohexane produced about a 15 per cent yield of mononitrocyclohexane.

IV. OXIDATION WITH NITROGEN TETROXIDE AND NITROGEN TRIOXIDE
(SEE TABLE 2)

From what has gone before it is obvious that many reactions involving nitrogen tetroxide are accompanied by more or less oxidation. There are other reactions in which oxidation products are the most important. There are also borderline examples which might be placed in more than one category.

A. Oxidation of paraffin hydrocarbons

Frolich, Harrington, and Waitt (65) made a careful study of the reaction of methane and nitrogen tetroxide when passed through Pyrex tubes at 440–680°C. and in the presence of various catalysts, including platinum, vanadium pentoxide, pumice, and nickel. Yields of formaldehyde somewhat under 25 per cent (based on the methane used) were formed. Methanol was not found among the products. Bibb (18) did similar work. The formation of formaldehyde from methane is the subject of a French patent (62) and a U.S. patent (9).

Chemists have been attracted by the hope of devising schemes of oxidizing paraffins to aliphatic acids. At best, one could expect a relatively complex mixture. Gränacher and Schaufelberger reported the oxidation of paraffin when treated with nitrogen tetroxide at 140°C. for 8 to 10 hr. to products completely soluble in alkali (77) but apparently did not identify any of them. This mixture may have contained nitroparaffins as well as carboxylic acids. According to another report (78) the paraffin was oxidized at 120–130°C. for 30 hr. The acids were esterified, and the resulting esters boiled from 37° to 300°C. at 23 mm. Apparently no distinct product was isolated. Undecane yielded a mixture of fatty acids, from which pelargonic acid was reported to have been isolated (77).

Schaarschmidt (171) also studied the action of nitrogen tetroxide with paraffin, but his success was apparently even less than that of Gränacher.

B. Reactions with oximes

Ponzio (133, 134, 142) studied the reactions of a number of oximes with nitrogen tetroxide. Scholl (196, 197) made similar studies. With the oxime of benzaldehyde and nitrogen tetroxide in dry ether (140) the reaction was reported as proceeding to give 16 per cent of benzaldoxime peroxide (I), 16 per cent of diphenylglyoxime peroxide (II), 12 per cent of benzaldehyde (III), and 50 per cent of dinitrophenylmethane (IV).

$$C_6H_5CH{=}NOH + N_2O_4 \rightarrow$$

$$
\begin{array}{cccc}
\begin{array}{c} C_6H_5CH{=}N{-}O \\ | \\ C_6H_5CH{=}N{-}O \end{array} & + & \begin{array}{c} C_6H_5C{=}N{-}O \\ | \quad | \\ C_6H_5C{=}N{-}O \end{array} & + \quad C_6H_5CHO \quad + \quad C_6H_5CH(NO_2)_2 \\
\text{I} & & \text{II} & \text{III} \qquad\qquad \text{IV} \\
\text{Benzaldoxime} & & \text{Diphenylglyoxime} & \text{Benzaldehyde} \quad \text{Dinitrophenyl-} \\
\text{peroxide} & & \text{peroxide} & \text{methane}
\end{array}
$$
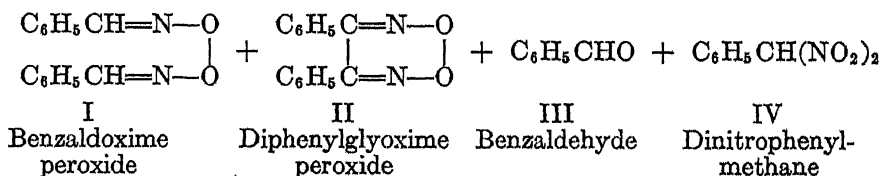
TABLE 2

Oxidation

COMPOUND OXIDIZED	OXIDE OF NITROGEN	PRODUCTS FORMED	REFERENCE
CH_4	N_2O_4	HCHO	(18, 65)
$C_6H_5CH_3$	N_2O_3	$(COOH)_2$, a dihydroxybenzoic acid, C_6H_5COOH, C_6H_5CHO, $o\text{-}NO_2C_6H_4CH_3$	(72, 102)
$C_6H_5CH_3$	N_2O_4	C_6H_5COOH, $(COOH)_2$, C_6H_5OH, C_6H_5CHO	(15, 72, 175)
$CH_3\text{—}C_6H_4\text{—}CH(CH_3)_2$	N_2O_3	[ring] COOH	(100, 101)
$p\text{-}ClC_6H_4CH_3$	N_2O_4	$p\text{-}ClC_6H_4COOH$	(175)
Anthracene	N_2O_3	Anthraquinone, red oil	(102)
Anthracene	N_2O_4	Anthraquinone	(15, 71, 92)
$o\text{-}CH_3C_6H_4NO_2$	N_2O_4	$o\text{-}NO_2C_6H_4COOH$	(15)
$m\text{-}CH_3C_6H_4NO_2$	N_2O_4	$m\text{-}NO_2C_6H_4COOH$	(15)
$p\text{-}CH_3C_6H_4NO_2$	N_2O_4	$p\text{-}NO_2C_6H_4COOH$	(15)
CH_3OH	N_2O_4	HCHO	(31)
C_2H_5OH	N_2O_4	CH_3CHO	(31)
$CH_3(CH_2)_3CH_2OH$	N_2O_4	$CH_3(CH_2)_3CHO$	(31)
$C_6H_5CH_2OH$	N_2O_4 or N_2O_3	C_6H_5COOH, C_6H_5CHO	(15, 31)
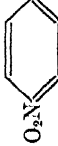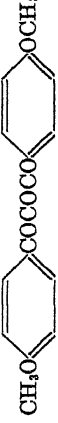
Compound	Reagent	Products	References
o-NO₂C₆H₄CH₂OH	N₂O₄	o-NO₂C₆H₄CHO	(31, 32)
p-NO₂C₆H₄CH₂OH	N₂O₄	p-NO₂C₆H₄CHO	(31)
C₆H₅CHO	N₂O₄	C₆H₅COOH	(15, 63, 64)
m-NO₂C₆H₄CHO	N₂O₄	m-NO₂C₆H₄COOH	(15)
p-NO₂C₆H₄CHO	N₂O₄	p-NO₂C₆H₄COOH	(15)
o-NO₂C₆H₄CHO	N₂O₄	o-NO₂C₆H₄COOH	(15)
HOCH₂CH(OC₂H₅)₂	N₂O₄	HOOCCH₂CH(OC₂H₅)₂	(114)
HOCH₂(CHOH)₄CHO (galactose)	N₂O₄	HOOC(CHOH)₄COOH (mucic acid)	(114)
α-Methylglucoside	N₂O₄	Glucuronic acid (as barium salt)	(114)
α-Methylgalactoside	N₂O₄	α-Methylgalacturonic acid	(114)
C₆H₅COCH₂COC₆H₅	N₂O₃	C₆H₅COCOCOC₆H₅, (C₆H₅CO)₂CH(N₂O₂)CH(COC₆H₅)₂	(245, 246)
O₂N–C₆H₄–COCH₂COC₆H₅	N₂O₃	O₂N–C₆H₄–COCOCOC₆H₅	(245)
CH₃O–C₆H₄–COCH₂CO–C₆H₄–OCH₃	N₂O₃	CH₃O–C₆H₄–COCOCO–C₆H₄–OCH₃	(245)
		(p-CH₃OC₆H₄CO)₂CH(N₂O₂)CH(COC₆H₄OCH₃-p)₂	
C₆H₅COCH₂COCH₃	N₂O₂	(C₆H₅CO)₂CH(N₂O₂)CH(COC₆H₅)₂	(245)
CH₃COCH₂COOC₂H₅	N₂O₂	CH₃COCOCOC₂H₅	(24)

TABLE 2—Continued

COMPOUND OXIDIZED	OXIDE OF NITROGEN	PRODUCTS FORMED	REFERENCE
$CH_2(COOC_2H_5)_2$	N_2O_3 or N_2O_4	$CH(NO)(COOC_2H_5)_2$, $CH(NO_2)(COOC_2H_5)_2$	(33, 34, 35, 36, 73, 195)
		$CO(COOC_2H_5)_2$, $C(NO_2)_2(COOC_2H_5)_2$	(31, 32)
$C_3H_7C(=NOH)CH_3$	N_2O_4	$C_3H_7CCH_3$ with NO and NO_2	(22)
CH_3—CH—C—CH_3 with CH_3, NOH	N_2O_4	N=O, CH_3—C—CH (CH_3), CH_3, NO_2	(22)
C_3H_7—C—C_3H_7 with NOH	N_2O_4	C_3H_7—C—C_3H_7 with N=O, NO_2	(22)
$C_6H_5CH=NOH$	N_2O_4	$C_6H_5CH(NO_2)_2$; $C_6H_5CH=N$—O, $C_6H_5C=N$—O; $C_6H_5CH=N$—O, $C_6H_5C=N$—O; C_6H_5CHO	(138, 139, 140, 141)

p-CH$_3$C$_6$H$_4$CH=NOH	N$_2$O$_4$	p-CH$_3$C$_6$H$_4$CH=N—O, p-CH$_3$C$_6$H$_4$CH=N—O (cyclic); p-CH$_3$C$_6$H$_4$C=N—O / p-CH$_3$C$_6$H$_4$C=N—O with NO$_2$; p-CH$_3$C$_6$H$_4$CHO; p-CH$_3$C$_6$H$_4$CH(NO$_2$)$_2$	(140)
C$_6$H$_5$—$\overset{\text{NOH}}{\underset{}{\text{C}}}$—C$_6H_5$	N$_2$O$_4$	C$_6$H$_5$—C—C$_6$H$_5$ (NO$_2$) or C$_6$H$_5$—C—ONO$_2$	(197)
p-CH$_3$OC$_6$H$_4$CH=NOH	N$_2$O$_4$	p-CH$_3$OC$_6$H$_4$CH(N$_2$O$_4$) and small amounts of other products	(140)
C$_6$H$_5$C(=NOH)COOH	N$_2$O$_4$	C$_6$H$_5$C=N—O, C$_6$H$_5$C=N—O	(142)
C$_6$H$_5$C(=NOH)CH$_2$OH	N$_2$O$_4$	C$_6$H$_5$CH(NO$_2$)$_2$	(142)
p-ClC$_6$H$_4$CH=NOH	N$_2$O$_4$	p-ClC$_6$H$_4$C(=NOH)NO$_2$, p-ClC$_6$H$_4$CH(N$_2$O$_4$)	(154)
m-NO$_2$C$_6$H$_4$CH=NOH	N$_2$O$_4$	m-NO$_2$C$_6$H$_4$C(=NOH)NO$_2$	(154)
CH$_3$C(=NOH)COOH	N$_2$O$_4$	CH$_3$C(=NOH)NO$_2$	(137)
C$_2$H$_5$(C=NOH)COOH	N$_2$O$_4$	C$_2$H$_5$(C=NOH)NO$_2$	(137)
CH(=NOH)COOH	N$_2$O$_4$	CH(=NOH)NO$_2$	(137)
CH$_2$(NO)COOC$_2$H$_5$	N$_2$O$_4$	C(=NOH)(NO$_2$)COOC$_2$H$_5$	(25)

TABLE 2—*Continued*

COMPOUND OXIDIZED	OXIDE OF NITROGEN	PRODUCTS FORMED	REFERENCE
$CH_2(NO)COOC_4H_9(iso)$	N_2O_3	$CHOCOOC_4H_9(iso)$	(25)
$C_2H_5CO(C=NOH)CH_3$	N_2O_4	$C_2H_5COCOCH_3$, $CH_3CH(NO_2)_2$, $CH_3C(N_2O_4)COC_2H_5$	(133)
$CH_3C(=NOH)COC_3H_7$	N_2O_4	$CH_3C(N_2O_4)COC_3H_7$	(143)
$C_2H_5COC(=NOH)C_3H_7$	N_2O_4	$C_2H_5COC(N_2O_4)C_3H_7$	(143)
$CH_3C(=NOH)COC_4H_9$	N_2O_4	$CH_3C(N_2O_4)COC_4H_9$	(143)
$CH_3C(=NOH)COC_5H_{11}$	N_2O_4	$CH_3C(N_2O_4)COC_5H_{11}$	(143)
$C_2H_5COC(=NOH)C_4H_9$	N_2O_4	$C_2H_5COC(N_2O_4)C_4H_9$	(143)
$CH_3C(=NOH)COC_4H_9(iso)$	N_2O_4	$CH_3C(N_2O_4)COC_4H_9(iso)$	(143)
$C_2H_5COC(=NOH)C_3H_7(iso)$	N_2O_4	$C_2H_5COC(N_2O_4)C_3H_7(iso)$	(143)
$CH_3C(=NOH)COC_5H_{11}(iso)$	N_2O_4	$CH_3C(N_2O_4)COC_5H_{11}(iso)$	(143)
$C_2H_5COC(=NOH)C_4H_9(iso)$	N_2O_4	$C_2H_5COC(N_2O_4)C_4H_9(iso)$	(143)
$CH_3C(=NOH)COC_4H_{13}(iso)$	N_2O_4	$CH_3C(N_2O_4)COC_4H_{13}(iso)$	(143)
$C_2H_5COC(=NOH)C_5H_{11}(iso)$	N_2O_4	$C_2H_5COC(N_2O_4)C_5H_{11}(iso)$	(143)
$C_6H_5COC(=NOH)C_6H_5$	N_2O_4	$C_6H_5COCOC_6H_5$, $C_6H_5COCOC_6H_4NO_2$-p, C_6H_5COOH, p-$O_2NC_6H_4COOH$	(134, 135)
$CH_3COC(=NOH)C_6H_5$	N_2O_4	$CH_3COCOC_6H_5$, $C_6H_5CH(N_2O_4)$	(136)

Compound	Reagent	Product	Reference
$CH_3C=NOH$	N_2O_4	$CH_3C=N-O-$	(197)
$C_2H_5C=NOH$	N_2O_4	$C_2H_5C=N-O-$	(197)
$CH_3C=NOH$	N_2O_4	$CH_3C=N-O-$, $CH_3C=N-O-$	(197)
$C_6H_5C=NOH$, $HC=NOH$	N_2O_4	$C_6H_5C=N-O-$, $HC=N-O-$	
$C_6H_5CH=NNHC_6H_5$	N_2O_4	$C_6H_5C(NO_2)=NNHC_6H_5$	(28, 29, 30)
$m\text{-}NO_2C_6H_4CH=NNHC_6H_5$	N_2O_4	$m\text{-}NO_2C_6H_4C(NO_2)=NNHC_6H_5$	(28, 29, 30)
$p\text{-}CH_3OC_6H_4CH=NNHC_6H_5$	N_2O_4	$p\text{-}CH_3OC_6H_4C(NO_2)=NNHC_6H_5$	(28, 29, 30)
$CH_2O_2 \cdot C_6H_3CH=NNHC_6H_5$ (piperonal phenyl-hydrazone)	N_2O_4	$CH_2O_2 \cdot C_6H_3C(NO_2)=NNHC_6H_5$	(28, 29, 30)
$CH_3OC_6H_4C(N=O)=NNHC_6H_5$	N_2O_3	$CH_3OC_6H_4C=NNHC_6H_5$, $C_6H_5N=NNO_2$	(13)

TABLE 2—Continued

COMPOUND OXIDIZED	OXIDE OF NITROGEN	PRODUCTS FORMED	REFERENCE
$\overset{\displaystyle N=O}{\underset{\displaystyle \vert}{m\text{-}NO_2C_6H_4C}}$=NNHC₆H₅	N_2O_8	$\overset{\displaystyle NO_2}{\underset{\displaystyle \vert}{m\text{-}NO_2C_6H_4C}}$=NNHC₆H₅	(13)
C_6H_5CH=CCl_2	N_2O_4	C_6H_5COH, $p\text{-}NO_2C_6H_4COOH$	(20)
C_6H_5CCl=CCl_2	N_2O_4	C_6H_5COOH, $p\text{-}NO_2C_6H_4COOH$	(20)
$(C_6H_5C_6H_4)_2C$=$C(C_6H_4C_6H_5)_2$	N_2O_4	$C_6H_5C_6H_4COC_6H_4C_6H_5$	(178)

Analogous reactions were reported for *p*-tolylaldoxime, anisaldoxime, benzophenone oxime, and acetophenone oxime. The ratios of the products (typified by I, II, III, IV) varied, depending upon the conditions and the specific oxime. There seems to be some doubt as to whether the dinitro compounds (IV) are true nitro compounds. Scholl (197) preferred to regard dinitrodiphenylmethane (V) as having the following structure:

$$C_6H_5-\underset{\underset{V}{\overset{|}{C_6H_5}}}{\overset{|}{C}}=N\overset{\overset{O}{\parallel}}{\underset{ONO_2}{\diagdown}}$$
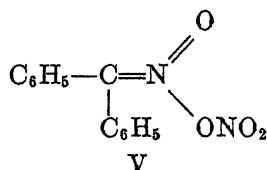
Dinitrodiphenylmethane

Neither Scholl nor Ponzio gave a rigid proof of the structure of this compound.

Scholl (196) concluded that the oximes of acetone, ethyl methyl ketone, and diethyl ketone reacted as indicated in the following equation:

$$\underset{CH_3}{\overset{CH_3}{\underset{|}{\overset{|}{C}}}}=NOH + N_2O_3 \text{ or } N_2O_4 \longrightarrow \underset{\underset{VI}{CH_3}}{\overset{CH_3}{\underset{|}{\overset{|}{C}}}}\overset{NO}{\underset{NO_2}{\diagdown}}$$
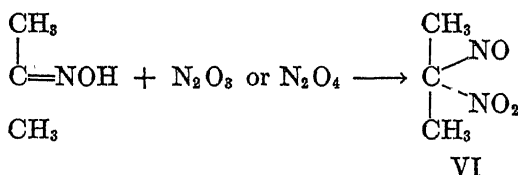
Compound VI was referred to as "propyl pseudonitrol" and was obtained in 25 per cent yield. A similar conclusion was reached by Born (22) for the reaction products of nitrogen tetroxide with methyl propyl ketoxime, isopropyl methyl ketoxime, and di-*n*-propyl ketoxime.

With the glyoximes such as dimethyl, methyl, ethylmethyl, and phenyl, the main reaction product with nitrogen tetroxide was the glyoxime peroxide. Formula VII represents the product formed from dimethylglyoxime.

$$\begin{array}{c} CH_3\,C=N-O \\ |\qquad\quad | \\ CH_3\,C=N-O \end{array}$$
VII
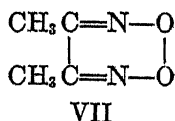
Ponzio concluded from his series of experiments that when compounds of type VIII were allowed to react with nitrogen tetroxide the major product was the

$$C_6H_5-\underset{\underset{VIII}{R}}{\overset{|}{C}}=NOH$$
VIII
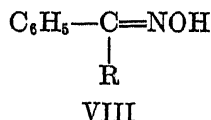
corresponding dinitromethane when R was H, —CH$_2$OH, or $CH_3\overset{\overset{O}{\parallel}}{C}$—, but not when R was —COOH, —CH$_3$, or —C$_6$H$_5$.

Ponzio (133, 134, 135, 136, 143) also studied the reactions of the monoximes of a few 1,2-diketones with nitrogen tetroxide. These reactions were carried out in cold dry ether, and the reaction mixtures were allowed to stand 1 hr. The product was washed with water and dried, and the ether was removed. The reactions were generally believed to proceed as follows:

$$
\underset{\substack{\parallel \quad \parallel}}{R-\overset{O}{C}-\overset{NOH}{C}-R'} + N_2O_4 \rightarrow \underset{\substack{\parallel \quad \parallel}}{R-\overset{O}{C}-\overset{(NO_2)_2}{C}-R'} + N_2O + H_2O + \underset{\substack{\parallel \quad \parallel}}{R-\overset{O}{C}-\overset{O}{C}-R'}
$$

$$
\downarrow
$$

$$
\underset{\substack{|\\ NO_2}}{R'-\overset{H}{\underset{|}{C}}-NO_2} + RCOOH
$$
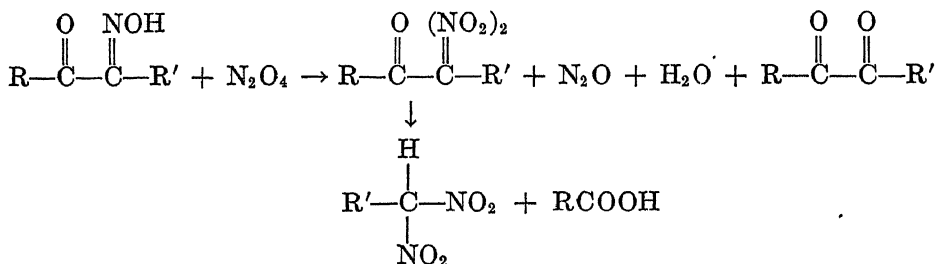
Nitrolic acids (IX) have been prepared by Ponzio (137) with nitrogen tetroxide reacting with α-isonitroso acids as indicated by the type equation:

$$
\underset{\substack{|\\ COOH}}{R-C{=}NOH} + N_2O_4 \xrightarrow{\text{ether}} \underset{\substack{\cdot\,|\\ COOH}}{R-C{=}(N_2O_3)}
$$

$$
\downarrow H_2O
$$

$$
R-C\overset{\displaystyle\nearrow NOH}{\underset{\displaystyle\searrow NO_2}{}} + CO_2
$$

$$
IX
$$
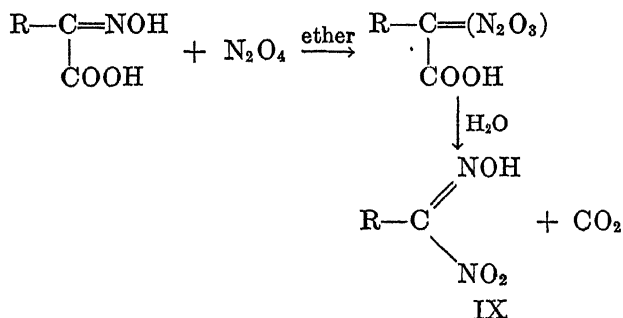
Starting with isonitrosoacetic acid or isonitrosopropionic acid, yields of more than 80 per cent of the corresponding nitrolic acids were produced.

Aromatic nitrolic acids were prepared by Ruggeri by allowing the oximes of aromatic aldehydes to react with nitrogen tetroxide in ether (154). For example, p-chlorobenzaldoxime gave (p-chlorophenyl)methylnitrolic acid (X):

$$
Cl{\Large\langle}\!\!=\!\!{\Large\rangle}C\overset{\displaystyle\nearrow NOH}{\underset{\displaystyle\searrow NO_2}{}}
$$

$$
X
$$
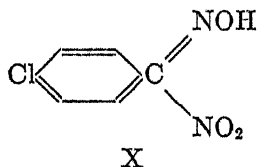
Boubeault and Wahl (25) allowed the ethyl ester of isonitrosoacetic acid to react with nitrogen tetroxide and obtained the corresponding isonitrosonitroacetic ester ($HON{=}C(NO_2)COOC_2H_5$) along with the ethyl ester of bisanhydronitroacetic acid.

C. Reactions with compounds containing active methylene groups

A useful laboratory reaction is the oxidation of malonic ester with nitrogen trioxide (33, 34, 35, 36, 74, 194) or nitrogen tetroxide (73) to produce ethyl

oxomalonate. The reagents are mixed while cold and allowed to warm gradually to room temperature, and the product is distilled. Explosive by-products are formed during the reaction, the amount depending on the conditions. Gilman and Johnson (73) obtained almost quantitative yields by adding a little sodium to the reaction mixture. They also showed that esters other than the ethyl ester could be used successfully to give analogous products. The reaction proceeds more satisfactorily with nitrogen tetroxide than with the trioxide.

The nitroso or isonitroso compound (XI) is generally believed to be the main by-product which tends to decompose upon distillation.

$$
\begin{array}{ccc}
\text{COOC}_2\text{H}_5 & \text{COOC}_2\text{H}_5 & \text{COOC}_2\text{H}_5 \\
| & | & | \\
\text{HCN}{=}\text{O} \quad \text{or} & \text{C}{=}\text{NOH} & \text{HCNO}_2 \\
| & | & | \\
\text{COOC}_2\text{H}_5 & \text{COOC}_2\text{H}_5 & \text{COOC}_2\text{H}_5 \\
\text{XI} & & \text{XII}
\end{array}
$$
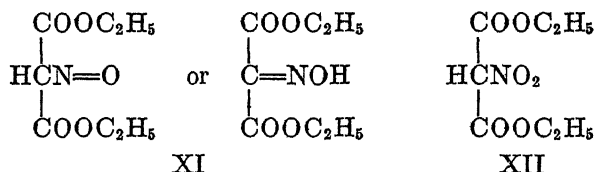
Curtis and Kostalek (36) believed that XII was formed during the reaction, and possibly ethyl dinitroacetate also.

If ethyl oxomalonate were needed on a large scale it should be possible to prepare it successfully by this method.

Another reaction related to this has been studied by Bouveault and Wahl, who converted acetoacetic ester with "nitrous fumes" into the diketone (XIII).

$$
\begin{array}{cc}
\text{O} \quad \text{O} \\
\| \quad \| \\
\text{CH}_3{-}\text{C}{-}\text{C}{-}\text{COOC}_2\text{H}_5 \\
\text{XIII}
\end{array}
$$
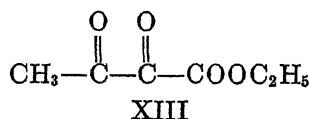
It was anticipated that ethyl methyl ketone would be converted to diacetyl and that ethyl cyanoacetate would be converted to ethyl ketocyanoacetate. These expectations were not realized under the conditions tried (150). Benzyl phenyl ketone and benzyl cyanide with nitrous acid (probably nitrogen trioxide) gave XIV and XV, respectively.

$$
\begin{array}{cc}
\text{O} \quad \text{NOH} & \text{NOH} \\
\| \quad \| & \| \\
\text{C}_6\text{H}_5{-}\text{C}{-}\text{C}{-}\text{C}_6\text{H}_5 & \text{C}_6\text{H}_5{-}\text{C}{-}\text{CN} \\
\text{XIV} & \text{XV} \\
\text{Benzil monoxime} & \alpha\text{-Cyanobenzaldoxime}
\end{array}
$$
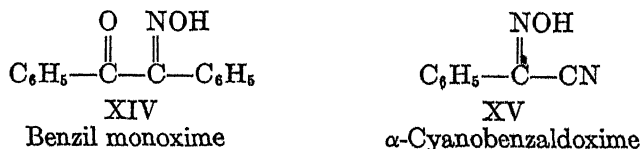
Wieland and Block (245, 246) studied the action of nitrogen trioxide with certain 1,3-diketones. With dibenzoylmethane the reaction proceeded as indicated:

$$
\begin{array}{c}
\text{O} \quad\quad \text{O} \\
\| \quad\quad\quad \| \\
2\text{C}_6\text{H}_5\text{CCH}_2\text{CC}_6\text{H}_5 \; + \; \text{N}_2\text{O}_3 \longrightarrow \\
\\
\text{O} \quad \text{O} \quad \text{O} \\
\| \quad \| \quad \| \\
\text{C}_6\text{H}_5\text{C}{-}\text{C}{-}\text{CC}_6\text{H}_5 \; + \; (\text{C}_6\text{H}_5\text{CO})_2\text{CH}(\text{N}_2\text{O}_2)\text{CH}(\text{COC}_6\text{H}_5)_2 \\
\text{XVI} \quad\quad\quad\quad\quad \text{XVII}
\end{array}
$$
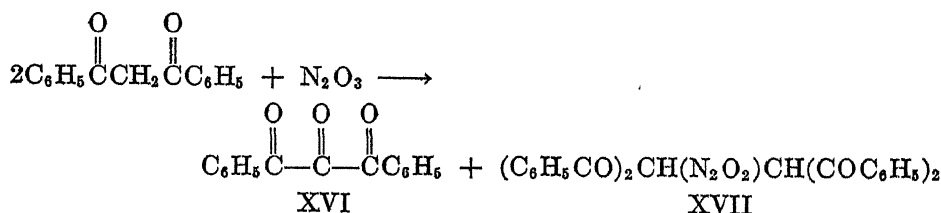
In addition to the above, about 15 per cent of an explosive product was formed to which the formula XVIII was assigned:

$$C_6H_5\overset{\overset{O}{\|}}{C}{-}\overset{\overset{O}{\|}}{C}{-}\overset{\overset{O}{\|}}{C}C_6H_5$$
$$N{=\!=\!=\!=}N$$

XVIII
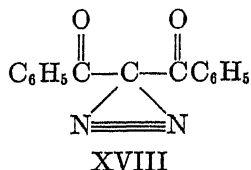
With benzoyl-p-nitrobenzoylmethane a quantitative yield of the corresponding triketone was formed. With di-p-methoxybenzoylmethane products corresponding to both XVI and XVII were formed. With acetylbenzoylmethane only the product analogous to XVI was obtained.

It would be interesting to try other compounds containing active methylene groups.

D. Miscellaneous oxidations

A number of simple oxidation reactions with nitrogen tetroxide have been carried out. Toluene gave a mixture of benzaldehyde and benzoic acid (72); o-, m-, and p-nitrotoluenes gave a low yield of the corresponding nitrobenzoic acids (15); benzyl alcohol gave benzaldehyde and benzoic acid (15, 31); o- and p-nitrobenzyl alcohols gave the corresponding nitro derivatives (31, 32); benzaldehyde was converted in 75 per cent yield to benzoic acid (15, 63, 64); o-, m-, and p-nitrobenzaldehydes gave the corresponding nitrobenzoic acids (15); 1-phenyl-2-dichloroethylene gave benzoic and p-nitrobenzoic acids; phenyltrichloroethylene gave benzoic and p-nitrobenzoic acids (20). Methods have been patented for the production of anthraquinone from anthracene and nitrogen tetroxide (71).

Yackel, Kenyon, and Unruh (220, 258) oxidized cellulose with dry nitrogen tetroxide to form a product readily soluble in 2 per cent sodium hydroxide, ammonium hydroxide, sodium carbonate, or warm pyridine. This oxidized cellulose is believed to have as high as 25 per cent carboxyl content, and it is believed that the primary hydroxyl groups are attacked preferentially. The material is especially interesting because it has a great affinity for basic dyes. Shorygin and Khait (199) and Maurer and Reiff (115) reported similar work with similar results. No nitration products were observed. Pinck (132) found it possible to nitrate cellulose quite satisfactorily by means of 85 to 99 per cent sulfuric acid and nitrogen tetroxide.

Maurer and Drefahl (114) found that nitrogen tetroxide oxidized galactose in chloroform to mucic acid in 75 per cent yields. α-Methylglucoside was oxidized to glucuronic acid (isolated as the barium salt) and α-methylgalactoside was oxidized to α-methylgalacturonic acid under similar conditions.

Indigo was allowed to react with nitrogen trioxide in 95 per cent alcohol. Ethyl benzoylformate was isolated (144, 145). When the reaction was carried out in ether, the unstable compound XIX was believed by Posner and Aschermann (144) to be formed.
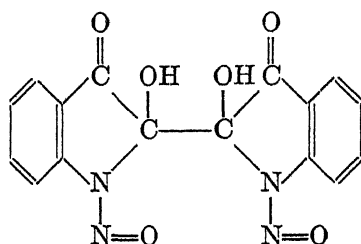
XIX

Compound XIX was converted into XX in low yield by warming with ethanol.
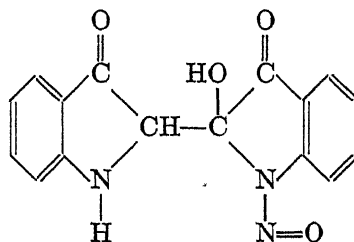
XX

Compound XX was treated with nitrogen trioxide in methanol and formed ethyl benzoylformate. *p*-Tolylindigo gave an analogous series of reactions.

Bamberger and Pemsel (13) allowed the phenylhydrazone of nitrosoanisaldehyde (XXI) to react with "nitrous fumes" and oxidized the nitroso group to the nitro group, forming XXII in about a 60 per cent yield. A trace of benzene-diazonium nitrate was also formed.
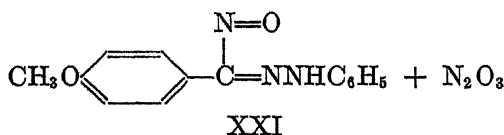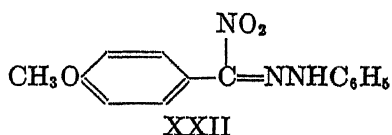
The phenylhydrazone of nitroso-*m*-nitrobenzaldehyde behaved in a similar manner.

Schlenk (178) added nitrogen tetroxide to tetrabiphenylethylene in carbon tetrachloride solution and reported an almost quantitative yield of the ketone XXIII.
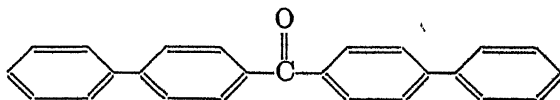
XXIII

An interesting type of oxidation with nitrogen tetroxide was carried out by Zincke (260). Tetrachlorocatechol, tetrabromocatechol, 2,3,6-trichlorohomo-catechol, and 2,3,4-trichlorohomocatechol were added to cold liquid nitrogen tetroxide. In the case of tetrachlorocatechol these reactions followed the course indicated:

$$
\begin{array}{c}
\text{OH} \\
\text{Cl} \diagdown \diagup \text{OH} \\
\text{Cl} \diagup \diagdown \text{Cl} \\
\text{Cl}
\end{array}
+ N_2O_4 \longrightarrow
\begin{array}{c}
\text{H} \quad \text{NO}_2 \ \text{Cl} \ \text{Cl} \quad \text{O} \\
\text{Cl}\overset{|}{\text{C}}\!-\!-\!\overset{|}{\text{C}}\!-\!-\!\overset{|}{\text{C}}\!=\!\overset{|}{\text{C}}\!-\!\text{C} \diagup\diagdown \\
\overset{|}{\text{NO}_2} \ \ \overset{|}{\text{Cl}} \qquad\qquad \text{COOH}
\end{array}
\cdot \ H_2O
$$
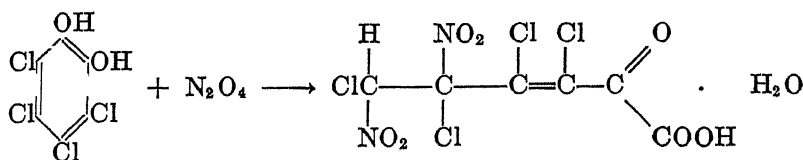
These changes were believed to proceed through the primary oxidation to the quinones, followed by the opening of the rings. The products were relatively unstable.

V. REACTIONS OF NITROGEN TETROXIDE AND NITROGEN DIOXIDE WITH COMPOUNDS CONTAINING CARBON–CARBON MULTIPLE BONDS (SEE TABLE 3)

The reactions of nitrogen tetroxide with compounds containing ethylenic or acetylenic linkages have received considerable attention. Investigators have no doubt been fascinated by the hope that these reactions would result in the formation of nitro compounds which might be valuable as explosives or might be reduced to useful amines. Up to the present time this hope has not been realized except in a few instances.

In general, the products from these reactions are unstable solids or intractable unstable oils from which it is often difficult or impossible to isolate pure compounds. Actually, the reports in the literature are conflicting and are confused by a lack of consistent nomenclature. Because of the unstable nature of many of the products, analyses are often open to doubt. Any interpretations based on such analyses must necessarily be scrutinized. In much of the earlier work the conditions of the experiments were not made clear. Even with the best attempts on record the products are complex, partly owing to polymerization, especially with the olefins of lower molecular weight.

In spite of the discouraging results up to the present time, it is still possible that with the appropriate choice of solvents and conditions some useful reactions may be found.

Looking at this problem first from a general point of view it would be expected that compounds with —C=C— linkages could react with nitrogen tetroxide in a variety of ways. On the basis of the structures suggested for nitrogen tetroxide the following possibilities have been suggested (174, 184, 233, 237, 242):

$$
\begin{array}{ccccc}
\text{H}\!-\!\overset{|}{\text{C}}\!-\!\text{NO} & & -\overset{|}{\text{C}}\!=\!\text{NOH} & -\overset{|}{\text{C}}\!-\!\text{NO}_2 & -\overset{|}{\text{C}}\!-\!\text{NO}_2 \\
& \text{or} & & & \\
-\overset{|}{\text{C}}\!-\!\text{ONO}_2 & & -\overset{|}{\text{C}}\!-\!\text{ONO}_2 & -\overset{|}{\text{C}}\!-\!\text{ONO}_2 & -\overset{|}{\text{C}}\!-\!\text{ONO} \\
\text{Nitrosonitrate} & & & \text{Nitronitrate} & \text{Nitronitrite} \\
\text{or} & & & & \\
\text{Nitrosate} & & & &
\end{array}
$$

$$
\begin{array}{cc}
-\overset{|}{\text{C}}\!-\!\text{NO}_2 & \qquad -\overset{|}{\text{C}}\!-\!\text{ONO} \\
-\overset{|}{\text{C}}\!-\!\text{NO}_2 & \qquad -\overset{|}{\text{C}}\!-\!\text{ONO} \\
\text{Dinitro} & \qquad \text{Dinitrite}
\end{array}
$$
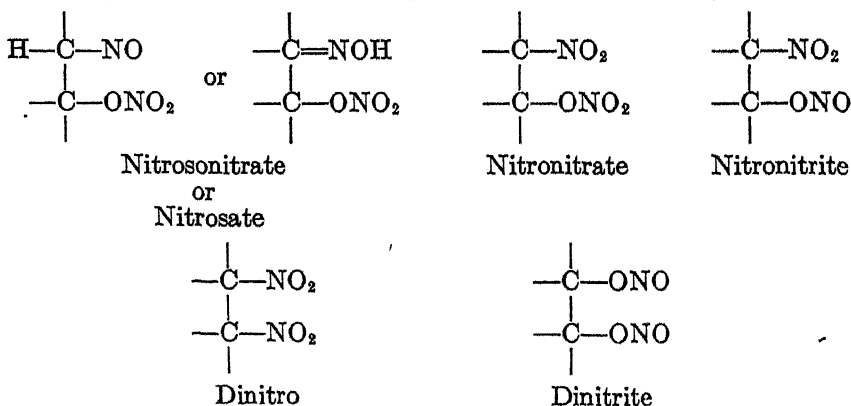
There seems to be no instance in which it has been shown clearly that the dinitrite was formed. The other four types may have been found. The nitronitrate could be formed by addition followed by oxidation.

A. Ethylene and simple ethylene derivatives

Sidorenko (208) passed oxides of nitrogen and ethylene through ether and collected the solid which formed. It was postulated that the solid formed was I.

$$CH_2 CH_2 NO_2$$
$$|$$
$$N_2 O_2$$
$$|$$
$$CH_2 CH_2 NO_2$$

I
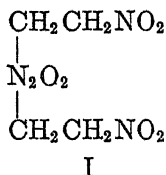
Heating I with concentrated hydrochloric acid gave carbon dioxide, oxides of nitrogen, and a carbonaceous residue. When warmed with amines I lost nitrous acid to give $(C_2H_4NO_2)_2$=NCH_2R. Dem'yanov (39) claimed that ethylene and nitrogen tetroxide reacted in ether to give $C_2H_4 \cdot N_2O_3$, which could be reduced with tin and hydrochloric acid to ethylenediamine. The production of nitrosites from ethylene and propylene, etc. was patented by Marshall (111).

Semenoff (198) probably succeeded in isolating a small yield of 1,2-dinitroethane from the reaction of ethylene and nitrogen tetroxide. In these experiments dry ethylene gas was passed through liquid nitrogen tetroxide or the reagents were warmed to 60–70°C.

As early as 1869 Kolbe (96) heated tetrachloroethylene and nitrogen trioxide in a sealed tube at 120°C. and obtained a product to which was ascribed the formula $C_2Cl_4(NO_2)_2$. This compound was not reduced. Argo and Donnelly (7) claimed 50 per cent yields of the same dinitro compound under about the same conditions. Biltz (20) claimed a good yield of sym-dinitrotetrachloroethane from tetrachloroethylene and nitrogen tetroxide when heated at 100°C. in a sealed tube for 3 hr. A similar reaction was claimed for tetrabromoethylene. The proof of the nature of these nitro compounds rested upon analyses. In view of much of the experience of later investigations it is questionable whether or not they were nitro compounds. Biltz (19) also believed that sym-diiododinitroethylene was produced from tetraiodoethylene and nitrogen tetroxide when they were heated in a sealed tube at 90°C. The proof was not rigid.

Burrows and Hunter (26) allowed sym-tetrachloroethylene to react with nitrogen tetroxide and reported the formation of sym-tetrachlorodinitroethane. With tribromoethylene 1,2-dinitrotribromoethane was formed. These claims also lack rigid proof. From 1,2-dichloroethylene and trichloroethylene no definite products were isolated except oxalic acid.

A number of investigations have been made of the reactions of nitrogen tetroxide with tetramethylethylene. Schmidt (190) believed that the main product of these reactions was II when ether was used as the solvent. His conclusion

TABLE 3

Ethylenic compounds

ETHYLENIC COMPOUND	OXIDE OF NITROGEN	PRODUCTS FORMED	REFERENCE
$CH_2=CH_2$	N_2O_3	$CH_2CH_2NO_2$ $\mid$ N_2O_2	(208)
$CH_2=CH_2$	N_2O_4	$CH_2CH_2NO_2$, $C_2H_4 \cdot N_2O_3$, $H_2C{-}CH_2$ $\mid\ \ \ \mid$ $NO_2\ NO_2$	(39, 198)
$C_2H_5CH=CH_2$	N_2O_2	$(C_4H_8 \cdot N_2O_3)_2$	(40)
$\overset{CH_3}{\mid}$ $CH_3C=CHCH_3$	N_2O_3	$\left[\begin{matrix} CH_3 \\ \mid \\ CH_3C{-}CHCH_3 \\ \mid\ \ \ \mid \\ ONO_2\ NO \end{matrix}\right]_2$ $\left[\begin{matrix} CH_3 \\ \mid \\ CH_3C{-}CHCH_3 \\ \mid\ \ \ \mid \\ NO_2\ NO \end{matrix}\right]_2$ $CH_3\qquad\qquad CH_3$ $\mid\qquad\qquad\ \ \mid$ $CH_3C{-}CHCH_3,\ \ CH_3C=CCH_3$ $\mid\ \ \ \mid\qquad\qquad \mid$ $NO_2\ NO_2\qquad\quad NO_2$	(122, 185, 186, 207, 214, 229, 231)

$CH_3C=CH_2$ (with CH_3)	N_2O_4	$\left[\begin{array}{c} CH_3 \\ CH_3C—CH_2 \\ ONO_2\ NO \end{array}\right]_2$, $\begin{array}{c} CH_3 \\ CH_3C=CHNO_2 \end{array}$	(123)
$CH_3C=CHC_2H_5$ (with CH_3)	N_2O_4	$CH_3—C—CH_2NO_2$ (with CH_3, NO_2), $CH_3—C—CH_2NO_2$ (with CH_3, ONO)	(95)
$CH_2C=CHCH_3$	N_2O_4	$\left[\begin{array}{c} CH_3 \\ CH_3C—CHCH_3 \\ ONO_2\ NO \end{array}\right]_2$, $\begin{array}{c} CH_3 \\ CH_3C—CHC_2H_5 \\ ONO_2\ NO \end{array}$, $\begin{array}{c} CH_3 \\ CH_3C—CHCH_3 \\ ONO\ NO_2 \end{array}$	(79, 80, 95, 119, 121, 125)
$CH_2=C—C=CH_2$ (with CH_3 CH_3)	N_2O_2	$C_6H_{10}\cdot N_2O_3$	(43)
$CH_3C=CCH_3$ (with CH_3 CH_3)	N_2O_4	$(CH_3)_2C——C(CH_3)_2$ (with $ONO_2\ NO_2$), $(CH_3)_2C——C(CH_3)_2$ (with $NO_2\ NO_2$)	(41, 124, 190)

TABLE 3—*Continued*
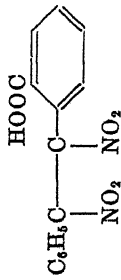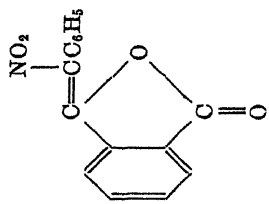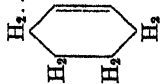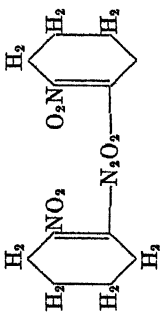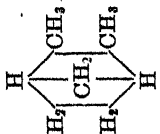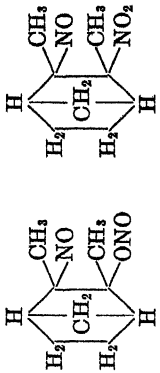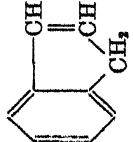
ETHYLENIC COMPOUND	OXIDE OF NITROGEN	PRODUCTS FORMED	REFERENCE
$C_6H_5CH=CH_2$	N_2O_3	$C_6H_5CH{-}CH_2$ or $C_6H_5CH{-}CH_2$ $\quad$ NO NO₂ $\quad\quad$ NO₂ NO $C_6H_5CHCH_2NO_2$ $\quad$ $C_6H_5CH=CHNO_2$ $\quad\quad$ N₂O₂ $C_6H_5CHCH_2NO_2$	(146, 210, 239)
$C_6H_5CH=CHC_6H_5$	N_2O_3	$C_6H_5CH{-}N=O \quad C_6H_5CH{-}N{-}O$ $\quad\quad$ O $\quad\quad$ or $\quad\quad$ O $C_6H_5CH{-}N=O \quad C_6H_5CH{-}N{-}O$ $C_6H_5CH{-}CHC_6H_5 \quad C_6H_5CH{-}CHC_6H_5$ $\quad$ NO₂ $\quad\quad\quad$ NO₂ NO₂ $C_6H_5CH{-}CHC_6H_5$ $\quad$ ONO NO₂	(67, 183, 243)
$C_6H_5CH=CHC_6H_5$	N_2O_4	$(C_6H_5CH=CHC_6H_5 \cdot N_2O_4)$ $C_6H_5CH{-}CHC_6H_5$ $\quad$ N₂O₂ NO₂ $C_6H_5CH{-}CHC_6H_5$ $C_6H_5CH{-}CHC_6H_5$ $\quad$ NO₂ NO₂	(184, 188)

$(C_6H_5)_2C=CH_2$	N_2O_4	$(C_6H_5)_2COHCH_2NO_2$
$(C_6H_5)_2C=CHC_6H_5$	N_2O_3	$(C_6H_5)_2C\underset{NO_2}{-}CHC_6H_5$
$CH_3O\overset{}{\underset{}{\bigcirc}}CH=CHCH_3$	N_2O_3	$CH_3O\bigcirc\underset{N_2O_2}{\overset{}{CH}}\underset{NO_2}{\overset{}{-CHCH_3}}$
		$CH_3O\bigcirc CH\underset{NO_2}{-}CHCH_3$
		$CH_3O\bigcirc C\overset{CCH_3}{\underset{N=N}{=}}$ $CH_3O\bigcirc C\overset{-CCH_3}{\underset{N=N}{=}}$
		$HO\ OH$
$CH_3O\bigcirc CH=CHCH_3$	N_2O_3	$CH_3O\bigcirc CH\underset{NO}{-}CHCH_3$ or $CH_3O\bigcirc C\overset{-CHCH_3}{\underset{NOH\ ONO}{=}}$
		ONO
$CH_3OCH_2CH=CH_2$	N_2O_3	Product on reduction with $SnCl_2$ and HCl gave $CH_3OCH_2CHCH_2NH_2$
		NH_2
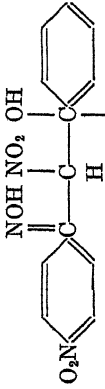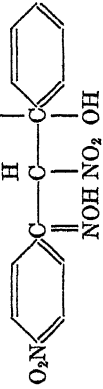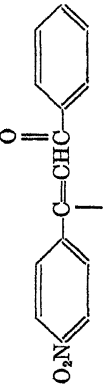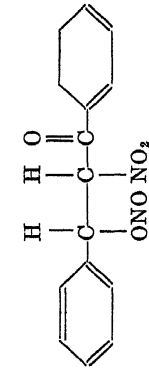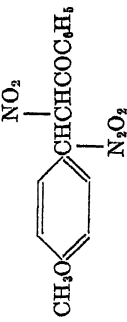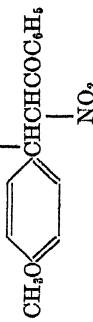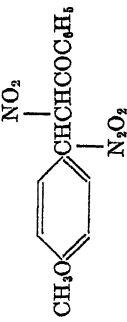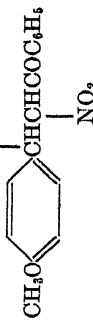
(250)
(204)
(237, 240)
(219)
(112)

TABLE 3—*Continued*

ETHYLENIC COMPOUND	OXIDE OF NITROGEN	PRODUCTS FORMED	REFERENCE
$C_6H_5CH=CH-$ (benzene ring with HOOC)	N_2O_3	$C_6H_5C(NO_2)-C(NO_2)$ (and ring structure: $C=C(NO_2)C_6H_5$, O, $C=O$ with benzene ring and HOOC)	(104)
(cyclohexene ring, H_2)	N_2O_3 or N_2O_4	(NO_2, H_2, H_2 substituted cyclohexene; O_2N-substituted, N_2O_2)	(243)
(ring with CH_3, CH_2, CH_3, H, H)	N_2O_3	(ring with CH_3, NO, CH_2, ONO, H; and ring with CH_3, NO, CH_2, CH_3, NO_2, H)	(129)
(benzene with $CH=$, CH, CH_3)	N_2O_3	$C_9H_8 \cdot N_2O_3$	(45)

$CH_2=C=CH_2$.	N_2O_3	$C_3H_4 \cdot N_2O_3$	(43)

$C_6H_5CH=CHCH=CHC_6H_5$.	N_2O_4	$C_6H_5CHCH=CHCHC_6H_5$
		    $\mid$ $\mid$
		    NO_2 NO_2
			(213, 254, 255)

$CH_2=C-C=CH_2$
    $\mid$ $\mid$
 C_6H_5 C_6H_5
	N_2O_4	$H_2C-C-CCH_2NO_2, H_2C=C-CCH_2NO_2$
		   $\mid$ $\mid$ $\mid$
		  NO_2 C_6H_5 C_6H_5 C_6H_5 C_6H_5
			(4)

CH_2
 HC CH
  $\parallel$ $\parallel$
 HC CH
	N_2O_3	CH_2
		 $CH-N_2O_2-CH$ CH
		               $\parallel$
		 $HC-CHNO_2$ O_2NCH CH
			(255)

CN
  $\mid$
 $C_6H_5C=CHCH=CHC_6H_5$
	N_2O_4	CN NO_2 NO_2
		  $\mid$ $\mid$ $\mid$
		 $C_6H_5C-CHCH-CHC_6H_5$
			(128)

C_6H_5
  $\mid$
 $C_6H_5CH=CHCH=CCOOH$
	N_2O_4	NO_2 NO_2
		  $\mid$ $\mid$
		 $C_6H_5CH=C-C=CHC_6H_5$
			(128)

$CH_2=CHCH_2CH_2CH=CH_2$.	N_2O_4	$C_6H_{10}(NO_2)_2$	(89, 94, 206)

$C_6H_5CH=CHCOCH=CHC_6H_5$.	N_2O_4	$C_6H_5CH-CHCOCH=CHC_6H_5$
		      $\mid$ $\mid$
		     NO_2 NO_2
			(243)

$Cl_2=Cl_2$	N_2O_4	$ClNO_2=ClNO_2$	(19)

TABLE 3—Continued

ETHYLENIC COMPOUND	OXIDE OF NITROGEN	PRODUCTS FORMED	REFERENCE
CCl_2=CCl_2	N_2O_4	NO_2 NO_2 Cl_2C—CCl_2	(7, 20, 26, 96)
CBr_2=CBr_2	N_2O_4	NO_2 NO_2 Br_2C—CBr_2	(20)
CBr_2=$CHBr$	N_2O_4	Br_2C—$CHBr$ NO_2 NO_2	(26)
CH_3CH=$CHCOOH$	N_2O_4	Product on reduction with Sn and HCl gave $CH_3CHOHCHNH_2COOH$	(49)
C_6H_5CH=$CHCHO$	N_2O_3	NO_2 C_6H_5C—C=CH C_6H_5C—CNO_2	(236)
CH_2=$CHCOOH$	N_2O_4	$C_3H_2O_2(NO_2)(OH)$, $C_3H_4O_2(NO_2)_2$	(48)
CH_3 CH_2=$CCOOH$	N_2O_4	Product on reduction with Sn and HCl gave NH_2CH_2CCOOH (with CH_3 and OH)	(50)

$CH_3CH=CHCOOH$.	N_2O_4	$CH_3CHOHCHNH_2COOH$ and $CH_3CHNH_2CHOHCOOH$ formed upon reduction with Sn and HCl	(1)
$(CH_3)_2C=CHCOOH$	N_2O_4	$(CH_3)_2C(OH)CHNH_2COOH$ and $(CH_3)_2CNH_2CHOHCOOH$ formed upon reduction with Sn and HCl	(1)
$CH_3(CH_2)_7CH=CH(CH_2)_7COOH$	N_2O_4	$CH_3(CH_2)_7CH\overset{NO_2}{-}CH\overset{ONO}{-}(CH_2)_7COOH$, $CH_3(CH_2)_7CH\overset{ONO}{-}CH\overset{NO_2}{-}(CH_2)_7COOH$	(52, 259)
$C_6H_5CH=CHCOOH$	N_2O_3	$C_6H_5CH=CHNO_2$	(56, 67)
$C_6H_5CH=\overset{CH_3}{\underset{\vert}{C}}COOH$	N_2O_3	$C_6H_5CH=\overset{CH_3}{\underset{\vert}{C}}NO_2$	(56)
$CH_2=CHCOOCH_3$	N_2O_4	$C_4H_6O_2(NO_2)(OH)$, $C_4H_6O_2(NO_2)_2$	(48)
$CH_2=CHCH_2CH_2COOC_2H_5$	N_2O_4	$C_7H_{12}O_2(NO_2)(OH)$, $C_7H_{12}O_2(NO_2)_2$	(51)
$C_6H_5CH=CHCH_2COOCH_3$	N_2O_3	$C_6H_5\overset{NO_2}{\underset{\vert}{C}H}\overset{N_2O_2}{\underset{\vert}{C}H}\overset{NO_2}{\underset{\vert}{C}H_2}COOCH_3$	(237)
$C_6H_5CH=CHCOCH_3$.	N_2O_3	$C_6H_5\overset{NO_2}{\underset{\vert}{C}H}\overset{N_2O_2}{\underset{\vert}{C}H}\overset{NO_2}{\underset{\vert}{C}H}COCH_3$ $C_6H_5C\overset{}{-}CHCOCH_3$ with $=NOH$ NO_2 $C_6H_5CHCHCOCH_3$	(237)

TABLE 3—*Continued*

ETHYLENIC COMPOUND	OXIDE OF NITROGEN	PRODUCTS FORMED	REFERENCE
	N_2O_3		(236)
	N_2O_3		(247)

(247)

(66)

(66)

$C_{15}H_{12}N_2O_4$

N_2O_3

N_2O_3

N_2O_3
or
N_2O_4

$$\underset{\underset{\text{II}}{\text{ONO ONO}}}{\overset{\overset{\text{CH}_3 \quad \text{CH}_3}{|\qquad\ |}}{\text{CH}_3-\text{C}\text{---}\text{C}-\text{CH}_3}} + 2\text{KOH} \longrightarrow \underset{\underset{\underset{\text{Pinacol}}{\text{III}}}{\text{OH} \quad \text{OH}}}{\overset{\overset{\text{CH}_3 \quad \text{CH}_3}{|\qquad\ |}}{\text{CH}_3-\text{C}\text{---}\text{C}-\text{CH}_3}} + 2\text{KNO}_2$$

that the solid compound II was the dinitrite was based on the observation that normal potassium hydroxide gave the quantity of potassium nitrite to be expected in accordance with the above reaction. The proof of the presence of pinacol was lacking. Schmidt also believed that he obtained a small amount of the dinitro derivative. Dem'yanov (41), on the other hand, believed that the main product was not the dinitrous ester but the nitronitrate (IV).

$$\underset{\underset{\text{IV}}{\text{ONO}_2 \quad \text{NO}_2}}{\overset{\overset{\text{CH}_3 \qquad \text{CH}_3}{|\qquad\qquad |}}{\text{CH}_3-\text{C}\text{----}\text{C}-\text{CH}_3}}$$
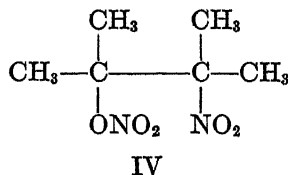
Dem'yanov (41) claimed the production of a very small quantity of *sym*-dinitrotetramethylethane from the reaction of nitrogen tetroxide and tetramethylethylene.

What appears to be the most thorough study of this reaction was made by Michael and Carlson (124). In ether solution they found 19.6–22 per cent of 2,3-dinitro-2,3-dimethylbutane. Without a solvent or with petroleum ether only low yields of the dinitro compound were formed. Under all experimental conditions IV was believed to be formed in various amounts depending upon the conditions. Compound IV and the dinitro derivative formed a double compound. Michael and Carlson concluded that Schmidt's dinitrous ester was not formed.

Michael and Carlson (123) also studied the products formed from isobutylene (2-methylpropene) and nitrogen tetroxide under a variety of conditions. The products from this reaction proved difficult to separate. The products believed to be formed were V, VI, VII and VIII.

$$\left[\underset{\underset{\text{V}}{\text{ONO}_2 \quad \text{NO}}}{\overset{\overset{\text{CH}_3}{|}}{\text{CH}_3-\text{C}\text{----}\text{CH}_2}}\right]_2 \qquad\qquad \underset{\underset{\text{VI}}{\text{NO}_2}}{\overset{\overset{\text{CH}_3}{|}}{\text{CH}_3-\text{C}=\text{CH}}}$$

"Bis(α,β-nitrosonitric ester)   "α-Nitroisobutene"
derivative of isobutene"

$$CH_3-\underset{\underset{NO_2}{|}}{\overset{\overset{CH_3}{|}}{C}}\text{——}\underset{\underset{NO_2}{|}}{CH_2}$$

VII

"α,β-Dinitroisobutane"

$$CH_3-\underset{\underset{ONO}{|}}{\overset{\overset{CH_3}{|}}{C}}\text{——}\underset{\underset{NO_2}{|}}{\overset{\overset{H}{|}}{CH}}$$

VIII

"α,β-Nitronitrous ester derivative of isobutene"
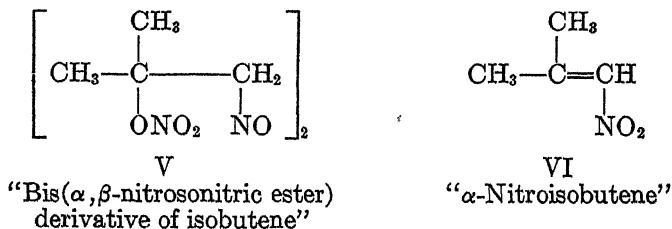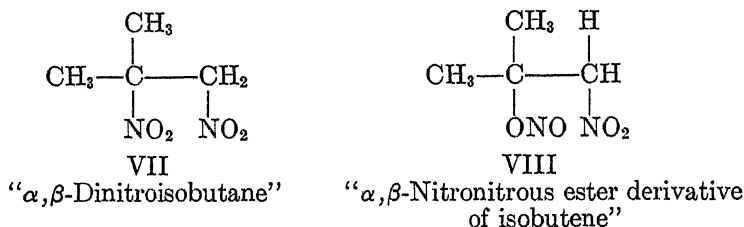
Product V was not separated when ether was used as a solvent. Without a solvent or with petroleum ether, V was formed to the extent of 13 per cent. When no solvent was used the products were largely oils. The liquid products formed in ether solution were more tractable and were distillable. The addition products in ether solution were not isolated directly but were reduced catalytically. Ammonia and β-hydroxyisobutylamine were found among the reduction products (16–23 per cent), indicating the presence of VIII; isobutylamine was produced by reduction, indicating the presence of VI (5–12 per cent); and isobutylenediamine was formed in quantities indicating at least 12 per cent of VII. This work verifies and adds to the findings of Sidorenko (207). The total yields of these products account for less than 50 per cent of the theoretical. It is probable that considerable polymerization or oxidation of the hydrocarbon took place. Again it is interesting to note the vital effect of the solvent on the course of the reaction.

Ipatieff and Ssolonima (93) reported V from the reaction of nitrogen tetroxide with "isobutene" (2-methylpropene), and analogous products from certain other ethylene derivatives.

Perhaps the reaction of trimethylethylene (amylene) with the oxides of nitrogen has been studied more than that of any other olefin. In 1861 Guthrie (79, 80) obtained a compound from amylene and nitrogen tetroxide to which he gave the formula $C_{10}H_{10}(NO_4)_2$. Translated to our present relative atomic weight system this formula would be $C_5H_{10}N_2O_4$. The latest findings indicate this to be the correct empirical formula for one of the products. Since both nitrogen trioxide and nitrogen tetroxide have been used in these studies, it would be well to consider them separately.

Wallach (229, 231, 232) obtained a 50 per cent yield of the nitric ester of 2-methyl-3-nitroso-2-butanol $(CH_3)_2C(ONO_2)CH(NO)CH_3$ (later shown to be the dimer) from trimethylethylene and "nitrous fumes" in acetic acid solution. This compound was referred to as trimethylethylene nitrosate. The presence of the $-ONO_2$ grouping was deduced from the reaction of the nitric ester with aniline to give aniline nitrate and

$$(CH_3)_2\underset{\underset{C_6H_5NH}{|}}{C}\text{——}\underset{\underset{NO}{|}}{CH}CH_3$$
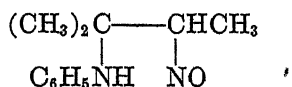
Similar experiments were carried out with other aromatic amines.

Schmidt (185, 186, 189) claimed yields as high as 84 per cent of what was assumed to be mainly the nitrous ester of 2-methyl-3-nitroso-2-butanol. This con-

clusion was reached on the basis of the color and on the gradual formation of a crystalline solid which was regarded as a dimer of the nitrous ester. On the basis of later work it is questionable if Schmidt's conclusions were correct.

Again the most complete study of the reaction of trimethylethylene with nitrogen trioxide was carried out by Michael and Carlson (122). They made clear that the "nitrous fumes" from arsenious oxide and nitric acid were variable in composition, depending upon the concentration of the nitric acid used and upon other conditions. This discovery explains why so many researches involving nitrogen trioxide led to differing results. In fact it was found to be difficult to get consistent yields even with the best efforts to control conditions.

Most of the experiments of Michael and Carlson were carried out using ether as the solvent. The products found are represented by formulas IX, X, XI, and XII.

$$
\begin{bmatrix} & CH_3 & \\ CH_3-C & & CHCH_3 \\ & ONO_2 & NO \end{bmatrix}_2 \qquad \begin{bmatrix} & CH_3 & \\ CH_3-C & & CHCH_3 \\ & NO_2 & NO \end{bmatrix}_2
$$

IX   X
                                (8.6 to 17.4 per cent)

$$
\begin{matrix} CH_3 & H \\ CH_3-C & C-CH_3 \\ NO_2 & NO_2 \end{matrix} \qquad \begin{matrix} CH_3 & \\ CH_3-C=C-CH_3 \\ & NO_2 \end{matrix}
$$

XI   XII
(10 to 20 per cent)   (10 to 20 per cent)
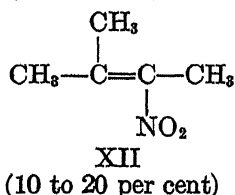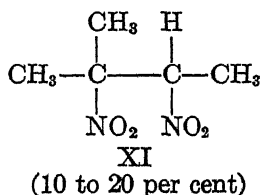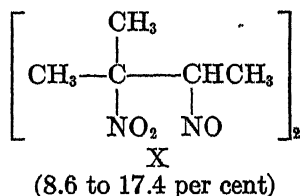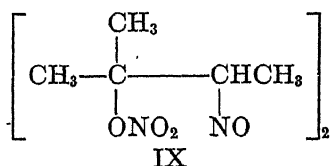
The dimeric nitric ester of 2-methyl-3-nitroso-2-butanol (IX) was shown to be present by catalytic reduction to 3-amino-2-methyl-2-butanol. Both X and XI were reduced to isoamylenediamine, and XII yielded 3-amino-2-methyl-butane upon reduction (44). X was oxidized to XI with nitrous fumes or ozone.

The liquid reaction products were distilled at low pressure, giving a volatile blue oil which contained X and XII and a higher boiling green oil which contained XI.

The reaction of trimethylethylene with nitrogen tetroxide was first studied by Guthrie (79, 80) and later by Tilden and Sudborough (214) and Miller (125), who obtained similar results. All subsequent investigations (95, 121, 186) agree that the solid derivative formed was the dimeric nitric ester of bis-2-methyl-3-nitroso-2-butanol. The yields of this ester have been reported from less than 1 per cent to 49 per cent depending upon the conditions.

Michael and Carlson (121) found the main reaction products to be XIII and XIV.

$$
\begin{bmatrix} & CH_3 & \\ CH_3-C & & CHCH_3 \\ & ONO_2 & NO \end{bmatrix}_2 \qquad \begin{matrix} & CH_3 & \\ CH_3-C & & CHCH_3 \\ & ONO & NO_2 \end{matrix}
$$

XIII   XIV
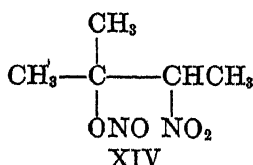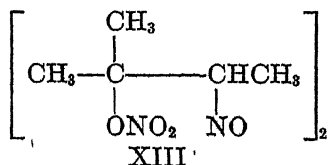
Very little of XIII was formed in ether, but in petroleum ether or without a solvent as high as 49 per cent of XIII was found. The liquid products from petroleum ether or without a solvent were so unstable that they were not identified. The liquid products formed when ether was used as a solvent were distillable. At least 35 per cent of this liquid product was shown to be XIV.

The presence of the —ONO_2 linkage in XIII was inferred from the reaction of XIII with sodium thiophenoxide to produce XV and sodium nitrate in quantitative yields.

$$CH_3-\underset{\underset{C_6H_5S}{|}}{\overset{\overset{CH_3}{|}}{C}}-\underset{\underset{H}{|}}{\overset{\overset{NO}{|}}{C}}-CH_3$$

XV
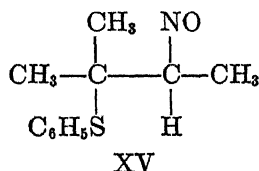
The presence of the —ONO linkage in XIV was also demonstrated by the reaction of XIV with sodium thiophenoxide to produce a quantitative yield of XVI and sodium nitrite.

$$CH_3-\underset{\underset{C_6H_5S}{|}}{\overset{\overset{CH_3}{|}}{C}}-\underset{\underset{NO_2}{|}}{\overset{\overset{CH_3}{|}}{GH}}$$

XVI
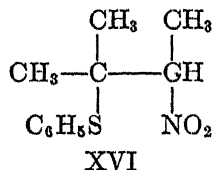
Monti (126) allowed octylene, diisobutylene, and hexadecylene to react with nitrogen trioxide and nitrogen tetroxide and obtained chiefly the nitronitrite and nitrosonitrate derivatives.

Diallyl and nitrogen tetroxide reacted in ether solution to give a substance which Henry (89) formulated as $C_6H_{10}(NO_2)_4$ and which presumably would now be written as $C_6H_{10}(NO_2)_2$. This product was not analyzed and no reactions of it were studied. Sidorenko (206) repeated this work and obtained a product which could be reduced to a diamine.

B. Aryl ethylenes

When styrene reacted with nitrogen trioxide (146) the product, according to Sommer (210) and Wieland (239), had the empirical formula $C_6H_5CH=CH_2N_2O_3$. Sommer suggested two possible structures, XVII and XVIII.

$$C_6H_5\,CH-CH_2 \qquad\qquad C_6H_5\,CH-CH_2$$
$$\underset{NO}{|}\;\;\underset{NO_2}{|} \qquad\qquad\underset{NO_2}{|}\;\;\underset{NO}{|}$$
$$\text{XVII} \qquad\qquad\qquad\qquad \text{XVIII}$$
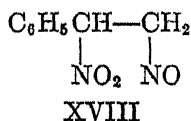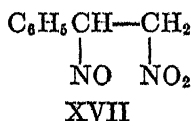
Wieland believed that the product was the dimeric form of XVII, or bis-1-nitroso-1-phenyl-2-nitroethane and wrote for it the formula XIX. Wieland referred to this substance as styrene pseudonitrosite, a name which has led to confusion. Compound XIX was found to be unstable.

$$C_6H_5CHCH_2NO_2$$
$$|$$
$$NO$$
$$|$$
$$NO$$
$$|$$
$$C_6H_5CHCH_2NO_2$$

XIX
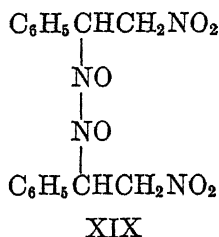
When refluxed with ethanol it changed to the oxime of α-nitroacetophenone; with concentrated hydrochloric acid it changed to α-nitroacetophenone, which further reacted to form benzoic acid and nitromethane.

Styrene, according to Priebs (146), reacted with nitrogen trioxide to yield 1-nitro-2-phenylethylene, after steam distillation of the product.

When stilbene reacted with nitrogen trioxide a solid product formed which Schmidt (183) claimed melted at 195–197°C. and Wieland (243) stated melted at 132°C. Apparently these investigators were working under different conditions; either they had different compounds or possibly they were working with mixtures. Both seemed to agree on the empirical formula $C_6H_5CH{=}CHC_6H_5N_2O_3$. Gabriel suggested the formula ($C_6H_5CH{=}CHC_6H_5N_2O_4$) (67). Schmidt regarded the product as a monomer; Wieland regarded it as a dimer and wrote for it the structural formula XX, which is analogous to XIX.

$$C_6H_5CH{-}CHC_6H_5$$
$$|\qquad|$$
$$NO\quad NO_2$$
$$|\qquad|$$
$$NO\quad NO_2$$
$$|\qquad|$$
$$C_6H_5CH{-}CHC_6H_5$$

XX
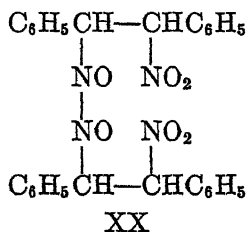
Schmidt formulated his compound as XXI or XXII.

XXI

XXII
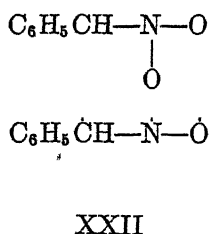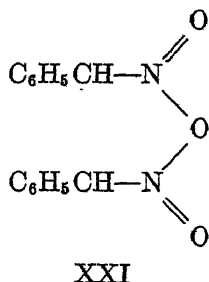
According to Schmidt (184), stilbene reacted with nitrogen tetroxide to produce 1,2-dinitro-1,2-diphenylethane.

Shilov (204) added oxides of nitrogen to triphenylethylene and obtained a good yield of what was presumed to be the 1,2-dinitro derivative.

C. Acetylenic compounds (see table 4)

Several examples have been described in which nitrogen trioxide or tetroxide reacted with compounds containing acetylenic linkages, forming nitro compounds. With phenylacetylene nitrogen tetroxide formed 1,2-dinitro-1-phenylethylene; 1,2-diphenylacetylene gave 1,2-dinitro-1,2-diphenylethylene, which upon reduction with zinc and acetic acid gave 2,3,5,6-tetraphenylpiperazine (182, 188, 248). As was expected, the 1,2-dinitro-1,2-diphenylethylene existed as both a *cis* and a *trans* isomer (182, 188).

Diiodoacetylene reacted with either nitrogen tetroxide or trioxide in ether solution to produce triiodonitroethylene (19). Some doubt exists regarding the nature of this product.

TABLE 4

Acetylenic compounds

ACETYLENIC COMPOUND	OXIDE OF NITROGEN	PRODUCTS FORMED	REFERENCE
$CI\equiv CI$	N_2O_3	$CI_2\!=\!CINO_2$	(19)
$CI\equiv CI$. . .	N_2O_4	$CI_2\!=\!CINO_2$	(19)
$C_6H_5C\equiv CH$.	N_2O_4	$C_6H_5C(NO_2)\!=\!CHNO_2$	(248)
$C_6H_5C\equiv CC_6H_5$ . . .	N_2O_3	$\begin{array}{cc} C_6H_5CNO_2 & C_6H_5CNO_2 \\ \parallel & \parallel \\ NO_2CC_6H_5 & C_6H_5CNO_2 \end{array}$	(182, 188)
$C_6H_5C\equiv CC_6H_5$	N_2O_4	$\begin{array}{c} C_6H_5C\!=\!=\!CC_6H_5 \;(cis \;and\; trans) \\ \vert \quad\;\; \vert \\ NO_2 \;\; NO_2 \end{array}$	(248)
$C_6H_5C\equiv CCOOC_2H_5$.	N_2O_4	$\begin{array}{c} C_6H_5C\!=\!=\!CCOOC_2H_5 \\ \vert \quad\quad\;\; \vert \\ NO_2 \;\; NO_2 \end{array}$	(241)

Wieland (241) reported the production of XXIII by the reaction of ethyl phenylpropiolate with nitrogen tetroxide in petroleum ether.

$$C_6H_5C\!=\!=\!CCOOC_2H_5$$
$$\vert \quad\quad\;\; \vert$$
$$NO_2 \;\; NO_2$$

XXIII
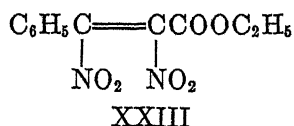
D. Ethylenic carbonyl compounds

Wieland (237, 247) studied the reaction of a series of compounds with nitrogen trioxide and in many cases obtained in low yields what he referred to as the corresponding pseudonitrosites. In this group were benzalacetone, methyl cinnamyl-

acetate, anisalacetophenone, 2-*p*-methoxyphenyl-1-methylethylene and anisal-acetone. To give a typical example, the product from benzalacetone was formulated as XXIV. Under the suggested terminology this would be called bis-1-acetyl-1-nitro-2-nitroso-2-phenylethane.

$$C_6H_5CH{-\!\!-\!\!-}CHCOCH_3$$
$$NO_2$$
$$N_2O_2$$
$$NO_2$$
$$C_6H_5CH{-\!\!-\!\!-}CHCOCH_3'$$
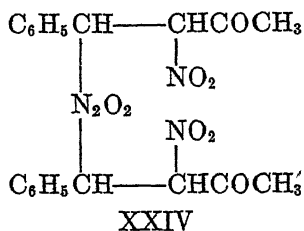
XXIV

In all cases Wieland studied several reactions of the products to substantiate his conclusions.

For cinnamaldehyde Wieland (237) regarded the first step as the formation of the monomeric nitronitroso derivative similar to XXIV. It was believed that it passed through the following sequence of changes:

$$C_6H_5CH{=}CHCHO + N_2O_3 \longrightarrow \left(\begin{array}{c} C_6H_5CH{-}CHCHO \\ NO \quad NO_2 \end{array} \right) \longrightarrow$$

$$\left(\begin{array}{c} NO_2 \; H \\ C_6H_5C{-}C{=}C{-}OH \\ NOH \end{array} \right) \longrightarrow \begin{array}{c} NO_2 \\ C_6H_5C{-}C{=}CH \\ N{-\!\!-\!\!-}O \end{array}$$
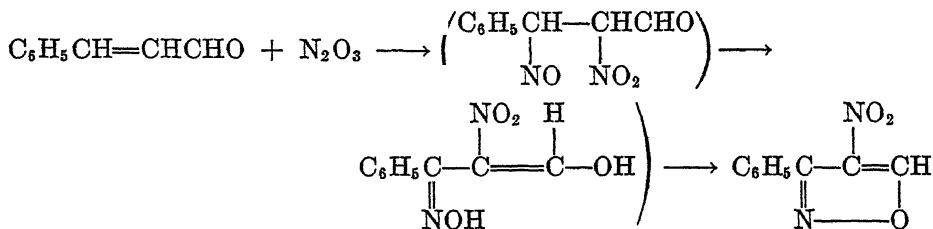
The end product was believed to be the 4-nitro-3-phenylisoxazole, which was obtained in 35 to 40 per cent yield. Wieland also reported the formation of a low yield of phenylnitroglyoxime peroxide (XXV).

$$C_6H_5C{-}CNO_2$$
$$N \quad N$$
$$O{-}O$$

XXV
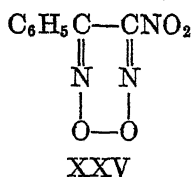
From benzalacetophenone with nitrogen trioxide Wieland (236) obtained an intermediate solid which upon boiling with ethanol gave the nitroisoxazole derivative XXVI, in which nitration took place in the benzene ring as well as reaction at the double bond.

$$NO_2$$
$$C_6H_5C{=}C$$
$$C{-}\!\!\!\!\bigcirc\!\!\!\!{-}NO_2$$
$$O{-}N$$
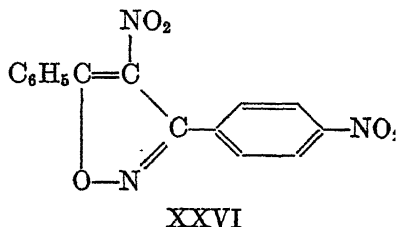
XXVI

On the basis of these experiments Wieland concluded (237, 247) that compounds of the type XXVII with nitrogen trioxide generally give the bisnitro-nitroso derivatives when R is positive in character, but fail to give the bisnitro-nitroso type when R is strongly negative.

$$C_6H_5CH{=}CHR$$
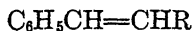
XXVII

When R is $-\overset{\overset{\textstyle O}{\|}}{C}-$, either the yields of the nitronitroso derivative are low or none at all can be isolated.

Egoroff (or Yegorov: 48, 49, 50, 51, 52, 259) carried out a series of studies on the reaction of unsaturated acids with nitrogen tetroxide. In general, relatively unstable addition products formed which were usually believed to be mixtures of the dinitro, isomeric nitronitrites, and hydroxynitro derivatives. The latter type was believed to be formed *via* the nitronitrite.

Upon reduction these addition products were transformed to diamino compounds or to amino alcohols. Although the yields were generally not stated, they must have been relatively low.

Since these addition compounds could be split at the position of the double bond by water or hydrochloric acid, it was proposed that such splitting could be used as a method of locating the position of the ethylenic linkage. The example of oleic acid will suffice to illustrate. The following sequence of reactions was suggested:

$$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH + N_2O_4 \xrightarrow{\text{petroleum ether}}$$

$$\underset{\substack{\text{XXVIII}}}{CH_3(CH_2)_7\underset{\substack{|\\ NO_2}}{CH}-\underset{\substack{|\\ ONO}}{CH}(CH_2)_7COOH} + \underset{\substack{\text{XXIX}}}{CH_3(CH_2)_7\overset{\substack{NO_2\\ |}}{CH}-\underset{\substack{|\\ ONO}}{CH}(CH_2)_7COOH}$$

$$2 \text{ moles XXVIII} + H_2O \xrightarrow[\text{160-170°C.}]{\text{18 hr.}}$$

$$2CH_3(CH_2)_7\underset{\substack{|\\ NO_2}}{CH}-\underset{\substack{\|\\ O}}{C}(CH_2)_7COOH + N_2O + H_2O$$

XXX

$$\Big\downarrow H_2O$$

$$\underset{\substack{\text{XXXI}}}{CH_3(CH_2)_7CHNO_2} + \underset{\substack{\text{XXXII}}}{COOH(CH_2)_7COOH}$$

2 moles XXIX + H_2O $\xrightarrow[\text{160–170°C.}]{\text{18 hr.}}$

$$\underset{XXXIII}{CH_3(CH_2)_7\overset{\overset{O}{\|}}{C}-\overset{\overset{NO_2}{|}}{C}H(CH_2)_7COOH} + N_2O + H_2O$$

$$\downarrow H_2O$$

$$\underset{XXXIV}{CH_3(CH_2)_7COOH} + \underset{XXXV}{NO_2CH_2(CH_2)_7COOH}$$
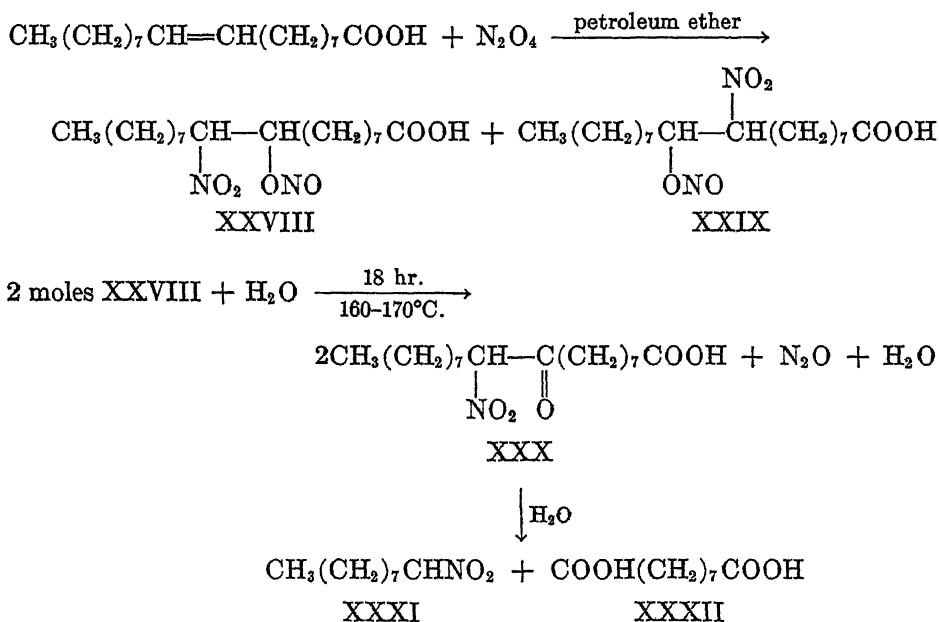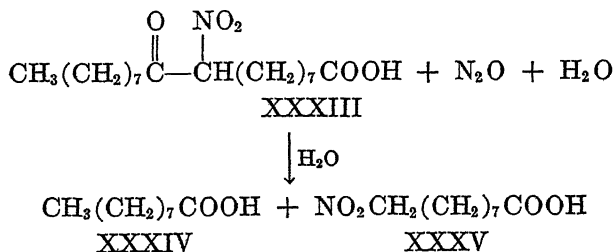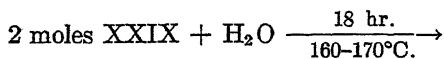
XXVIII and XXIX when heated with concentrated hydrochloric acid in a sealed tube for 3–5 hr. were considered as first reacting as above with water to give XXX, XXXI, XXXII, XXXIII, XXXIV, and XXXV. Then XXXI and XXXV reacted further:

$$XXXI \rightleftharpoons CH_3(CH_2)_7C\overset{\overset{OH}{\diagup}}{\underset{\diagdown NOH}{}} + H_2O \xrightarrow{HCl} CH_3(CH_2)_7COOH + NH_2OH$$

$$XXXV \rightleftharpoons \underset{HON}{\overset{HO}{\diagdown}}C(CH_2)_7COOH + H_2O \xrightarrow{HCl}$$

$$COOH(CH_2)_7COOH + NH_2OH$$
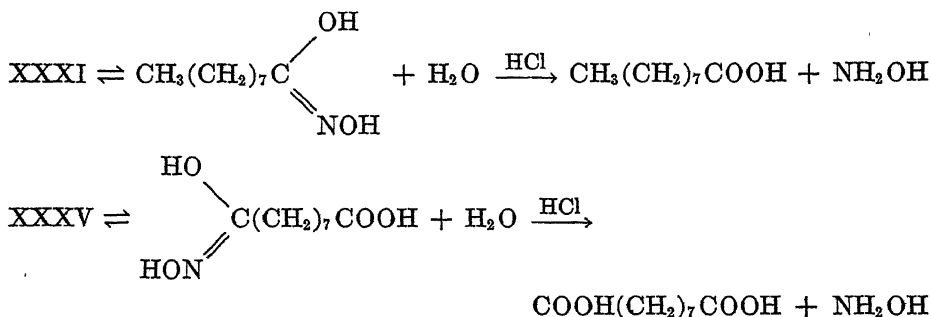
Accordingly, with concentrated hydrochloric acid the final products formed are azelaic and pelargonic acids, thus fixing the position of the double bond at 9,10, which is the same position as deduced by ozonolysis. This same type of bond location was done with other examples. Unfortunately the yields of the products were not stated. It may be guessed that they were discouragingly low, because apparently no one has attempted to extend the method. If conditions could be realized for obtaining reasonably good yields, this idea might be useful.

With cinnamic acid and nitrogen trioxide, Erdman (56) obtained as the only isolable product 1-nitro-2-phenylethylene. With α-methylcinnamic acid the analogous nitro derivative was obtained. Abderhalden (1) treated dimethyl-acrylic acid with nitrogen tetroxide and obtained results analogous to those of Egoroff.

E. Conjugated systems

Some cases of the reaction of nitrogen tetroxide with conjugated systems are recorded. Wieland (254, 255) observed the formation of 1,4-dinitro-1,4-di-phenyl-2-butene when either nitrogen trioxide or tetroxide was added to 1,4-diphenyl-1,3-butadiene. The addition product could be reduced to the corresponding diamine in poor yields. Thorpe and Farmer (213) made a similar claim.

Neber and Paeschke (128) claimed 1,2-addition to 1-cyano-1,4-diphenyl-1,3-butadiene to obtain 1-cyano-1,4-diphenyl-3,4-dinitro-1-butene. Other examples studied were less conclusive with regard to 1,2- or 1,4-addition. Franklin and Wilkins (61) believed they obtained 1,4-dinitro-2-butene from the reaction of nitrogen tetroxide and 1,3-butadiene when these substances were allowed to react in various solvents or in the vapor phase. Dinitro derivatives were reported from other conjugated diolefins.

Allen *et al.* (4) observed both 1,2- and 1,4-addition of nitrogen tetroxide to 2,3-diphenyl-1,3-butadiene, giving rise to XXXVI and XXXVII.

$$O_2NCH_2C\!\!=\!\!=\!\!CCH_2NO_2 \qquad\qquad CH_2\!\!=\!\!C\!\!-\!\!-\!\!\overset{\displaystyle NO_2}{\underset{\displaystyle\;}{C}}CH_2NO_2$$

$$\underset{\displaystyle C_6H_5}{|}\;\;\underset{\displaystyle C_6H_5}{|} \qquad\qquad \underset{\displaystyle C_6H_5}{|}\;\;\underset{\displaystyle C_6H_5}{|}$$

<div align="center">

XXXVI   XXXVII

(m.p. 151°C.)   (m.p. 192°C.)

</div>
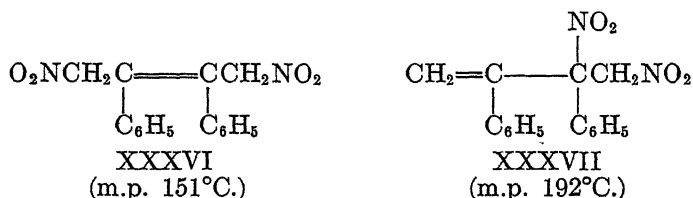
Ozonolysis of XXXVII produced formaldehyde, and oxidation with permanganate gave benzil. When XXXVII was dissolved in concentrated sodium methoxide a yellow crystalline sodium salt resulted, which upon acidification with acetic acid gave XXXVI. When the sodium salt of XXXVI was acidified, XXXVII was obtained.

F. Miscellaneous ethylenic compounds

Propadiene (43) with nitrogen trioxide gave a crystalline nitrosite having the formula $C_3H_4N_2O_3$. The structural formula was not elucidated. Dimethylbutadiene gave a crystalline nitrosite, $C_6H_{10}N_2O_3$, which was reduced to an amine. The structures of these compounds were not stated.

1-Butene (40) reacted with nitrogen trioxide to give $(C_4H_8N_2O_3)_2$, which presumably was the bisnitrosonitro derivative. A residue was also formed which upon reduction gave a diamine, $C_4H_8(NH_2)_2$, and *n*-butyraldehyde.

Anethole reacted with sodium nitrite and acetic acid at 50–60°C. to give XXXVIII and XXXIX (240).

$$CH_3O\!\!-\!\!\langle\;\rangle\!\!-\!\!\overset{}{\underset{\displaystyle NOH}{C}}\!\!-\!\!-\!\!\overset{}{\underset{\displaystyle NOH}{C}}CH_3 \qquad\qquad CH_3O\!\!-\!\!\langle\;\rangle\!\!-\!\!\overset{}{\underset{\displaystyle N}{C}}\!\!-\!\!\overset{}{\underset{\displaystyle N}{C}}CH_3$$

<div align="center">

XXXVIII   XXXIX

</div>

When the same reaction was carried out in the cold, the bisnitrosonitro compound XL was formed.

$$\left[CH_3O\!\!-\!\!\langle\;\rangle\!\!-\!\!\overset{}{\underset{\displaystyle NO}{C}}\!\!=\!\!=\!\!\overset{}{\underset{\displaystyle NO_2}{C}}HCH_3\right]_2$$

<div align="center">

XL

</div>

Toennies (219) apparently obtained by a similar reaction a compound with the same empirical formula but preferred to consider it the nitrosonitrous compound XLI.

$$CH_3O\langle\hspace{-0.5em}\bigcirc\hspace{-0.5em}\rangle CH—CHCH_3$$
$$\hspace{4em}|\hspace{1.5em}|$$
$$\hspace{4em}NO\hspace{0.8em}ONO$$

<div align="center">XLI</div>

The conditions of Toennies' experiment were vaguely stated.

Angeli (5, 6) concluded that compounds such as apiole, safrole, and eugenole containing the grouping —CH_2—CH=CH_2 did not react with nitrous acid (probably nitrogen trioxide) to give solid derivatives, but that the corresponding iso-compounds containing —CH=CH—CH_3 did give solid derivatives, presumably of the nitronitrite type.

Wieland (255) allowed cyclopentadiene to react with nitrogen trioxide and obtained an unstable solid derivative. In spite of its instability and the difficulty of its analysis the formula XLII was suggested, probably more because of analogy with other "pseudonitrosites" obtained by Wieland.

$$HC\overset{CH_2}{\diagup}\hspace{0.5em}CH—N_2O_2—CH\hspace{0.5em}\overset{CH_2}{\diagup}\hspace{0.5em}CH$$
$$HC———CHNO_2\hspace{0.5em}O_2NCH———CH$$

<div align="center">XLII</div>

Rule (155) and Wieland (255) studied the action of nitrogen trioxide with dicyclopentadiene. Rule gave XLIII for the formula of the product, which is

$$\left[\begin{array}{c}CH_2—CH—CH—CH_2\\HC\diagup\hspace{2em}\diagdown CHNO_2\\CH—CH—CH—CH\\|\\NO\end{array}\right]_2$$

<div align="center">XLIII</div>

the bisnitronitroso derivative, the type so often postulated by Wieland for the addition product of nitrogen trioxide to ethylenic bonds.

Cyclohexene (176) with dry nitrogen tetroxide in cold petroleum ether gave about a 25 per cent yield of the bisnitrosonitro derivative and oily products.

1,3-Cyclohexadiene with nitrogen trioxide in chloroform gave an intermediate which, when reduced with tin and hydrochloric acid, gave $C_6H_8(NH_2)_2 \cdot 2HCl$.

Dihydronaphthalene dissolved in acetone solution and treated with nitrogen tetroxide gave an unidentified solid, which on treatment with alcoholic potassium hydroxide yielded 2-nitro-3,4-dihydronaphthalene.

Gabriel (66, 67) allowed benzylidenephthalide (XLIV) to react with both nitrogen trioxide and tetroxide and obtained the relatively unstable XLV in both cases.

XLIV   XLV

Compound XLV lost nitrous acid in boiling benzene to give XLVI.

XLVI

According to Dennstedt (45) indene and coumarone reacted in cold ether solution with nitrogen trioxide to form the corresponding nitrosonitrite derivatives, along with oily products. In a similar manner santene gives the santene nitrosonitrite (XLVII) (129). Compound XLVII can be converted by reduction to XLVIII and can be oxidized to XLIX.

XLVII   XLVIII

XLIX
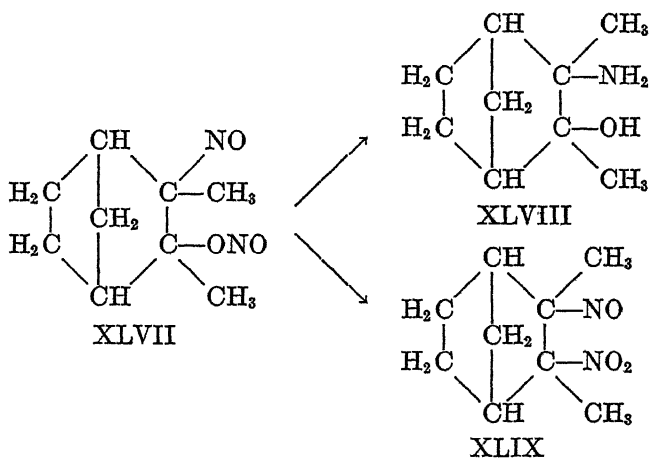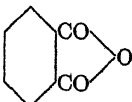
The reaction of benzaldiacetyl monoxime with nitrogen trioxide in dry ether solution stands out as an unusual case. Diels (46) ascribed formula L to

the unstable solid derivative thus obtained. A series of reactions of L were studied to elucidate its structure.

$$C_6H_5CHCH(OH)COCH_2CN$$
$$|$$
$$N_2O_2$$
$$|$$
$$C_6H_5CHCH(OH)COCH_2CN$$
$$L$$
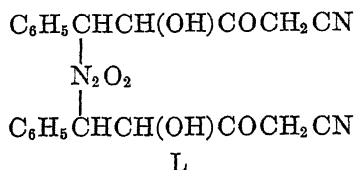
The only case found in which an unsaturated ether was allowed to react with nitrogen trioxide was that of methyl allyl ether. An undetermined nitro-nitrosopropyl ether was formed, which upon reduction gave methyl β,γ-diamino-propyl ether.

TABLE 5

Alkali metal salts of organic acids

ORGANIC ACID SALT	OXIDE OF NITROGEN	PRODUCTS FORMED	REFERENCE
CH₃COONa	N_2O_4	$(CH_3CO)_2O$	(152, 153)
C_2H_5COONa	N_2O_4	$(C_2H_5CO)_2O$	(152, 153)
C_3H_7COONa	N_2O_4	$(C_3H_7CO)_2O$	(152, 153)
CH₂COONa CH₂COONa	N_2O_4	$\begin{array}{c}CH_2CO\\ \mid\quad\quad\rangle O\\ CH_2CO\end{array}$	(151)
⬡COONa ⬡COONa	N_2O_4	⬡ CO⟩O CO	(151)

Considerable use of the oxides of nitrogen has been made in the separation and detection of terpenes (27, 37, 47, 58, 59, 68, 107, 228, 230). The oxides of nitrogen are added to the natural mixture to produce solid derivatives. These compounds and their reactions are usually not important except for identification purposes. The literature describing these compounds is confusing, because the structures of some terpenes previously accepted have been shown to be in error. Since this field is so confusing and since the compounds formed are not of general interest, no attempt has been made to collect and discuss the reactions of the oxides of nitrogen with terpenes.

A similar statement can be made for the studies conducted with oxides of nitrogen and rubber. After examining several papers by Harries (81, 82, 83, 84, 85) and by others (2, 3, 55, 75) and after observing the inconclusive nature of this work, no attempt was made to collect all the references on this subject.

VI. REACTIONS WITH ALKALI METAL SALTS OF ORGANIC ACIDS (SEE TABLE 5)

Rodionov and Oblitseva (152, 153) observed that good yields of acetic, propionic, and butyric anhydrides could be obtained by heating the dry sodium salts of the corresponding acids with nitrogen tetroxide. They expressed the reaction for sodium acetate as follows:

$$2CH_3COONa + 2N_2O_4 \rightarrow (CH_3CO)_2O + 2NaNO_3 + N_2O_3$$

This same technique was tried by Riebsomer and Reinecke (151), using the sodium salts of succinic and phthalic acids. The corresponding anhydrides were obtained in yields of 75 per cent or more. This approach to anhydride formation might be of interest.

VII. REACTIONS WITH ORGANOMETALLIC COMPOUNDS (SEE TABLE 6)

Wieland (238) found that ethylmagnesium iodide in cold ether reacted very vigorously with nitrogen tetroxide. After hydrolysis and extraction with ether, diethylhydroxylamine was obtained. No analogous compound was produced from aryl Grignard reagents (249). This method might be useful for the synthesis of special hydroxylamines which are not readily obtainable by other methods.

Various aromatic organometallic compounds have been allowed to react with nitrogen trioxide or with mixtures of nitric oxide and nitrogen dioxide simultaneously (11, 97, 110, 209). In many instances good yields of the aromatic diazonium nitrates were produced. Thus diphenylmercury gave benzenediazonium nitrate with a yield of 85 per cent; tetraphenyltin, 40 per cent; tetraphenyllead, 100 per cent; phenylmagnesium bromide, 15 per cent; triphenylbismuth, 54 per cent; di-p-tolylmercury, 51 per cent. Aryl metal nitrates and aromatic nitroso compounds were formed simultaneously. Dimethylmercury gave an explosive crystalline product (12).

VIII. MISCELLANEOUS REACTIONS (SEE TABLE 7)

Schmidt (191, 192, 193, 194) allowed various mono-α-substituted acetoacetic esters to react with nitrogen trioxide and obtained generally the corresponding relatively unstable blue α-nitroso derivatives. The general reaction may be written:

$$\underset{\displaystyle \quad}{CH_3CO\overset{\displaystyle R}{\overset{\displaystyle |}{C}HCOOC_2H_5}} + N_2O_3 \rightarrow CH_3CO\overset{\displaystyle R}{\underset{\displaystyle NO}{\overset{\displaystyle |}{\underset{\displaystyle |}{C}}}}COOC_2H_5$$
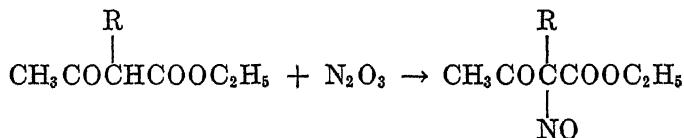
When both α hydrogens were substituted with alkyl groups no action took place.

α-Nitroso or -isonitroso compounds were also formed from ethyl propionate, isoamyl acetate, and other esters. Schmidt's general conclusion was that these

TABLE 6

Organometallic compounds
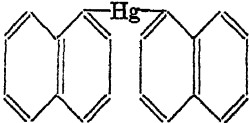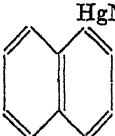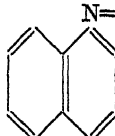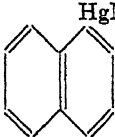
ORGANOMETALLIC COMPOUND	OXIDE OF NITROGEN	PRODUCTS FORMED	REFERENCE
$Hg(C_6H_5)_2$	N_2O_3	$HgC_6H_5NO_3$, $C_6H_5N=NNO_3$, C_6H_5NO	(11, 110)
$Hg(C_6H_5)_2$	N_2O_4	$HgC_6H_5NO_3$, C_6H_5NO	(11)
$(p\text{-}CH_3C_6H_4)_2Hg$	N_2O_3	$p\text{-}CH_3C_6H_4HgNO_3$, $p\text{-}CH_3C_6H_4N=NNO_3$	(97)
$(p\text{-}CH_3C_6H_4)_2Hg$	N_2O_4	$p\text{-}CH_3C_6H_4HgNO_3$, $p\text{-}CH_3C_6H_4NO$	(97)
$(o\text{-}CH_3C_6H_4)_2Hg$	N_2O_3	$o\text{-}CH_3C_6H_4HgNO_3$, $o\text{-}CH_3C_6H_4N=NNO_3$	(97)
$(o\text{-}CH_3C_6H_4)_2Hg$	N_2O_4	$o\text{-}CH_3C_6H_4HgNO_3$, $o\text{-}CH_3C_6H_4NO$	(97)
(di-naphthyl mercury structure)	N_2O_3	(naphthyl-$HgNO_3$), (naphthyl-$N=N-NO_3$)	(97)
	N_2O_4	(naphthyl-$HgNO_3$)	(97)
$(C_6H_5)_4Sn$	N_2O_3	$C_6H_5N=NNO_3$	(110)
$(C_6H_5)_3SnCl$	N_2O_3	$C_6H_5N=NNO_3$	(110)
$(C_6H_5)_2SnCl_2$	N_2O_3	$C_6H_5N=NNO_3$	(110)
$C_6H_5SnCl_3$	N_2O_3	$C_6H_5N=NNO_3$	(110)
$(C_6H_5)_4Pb$	N_2O_3	$C_6H_5N=NNO_3$	(110)
$(C_6H_5)_3PbCl$	N_1O_3	$C_6H_5N=NNO_3$	(110)
$(C_6H_5)_3Bi$	N_2O_3	$C_6H_5N=NNO_3$	(110)
$(C_6H_5)_2TiCl$	N_2O_4	$C_6H_5N=NNO_3$	(110)
C_6H_5MgBr	N_2O_4	$C_6H_5N=NNO_3$	(110)
C_2H_5MgI	N_2O_4	$(C_2H_5)_2NOH$ (after hydrolysis)	(238)

TABLE 7
Miscellaneous
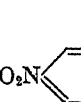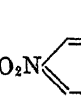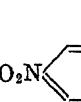
COMPOUND	OXIDE OF NITROGEN	PRODUCTS FORMED	REFERENCE
Maleic acid	N_2O_3	Fumaric acid	(180)
Oleic acid	N_2O_4	Elaidic acid	(76, 118)
$C_6H_5NH_2$	N_2O_4	$C_6H_5N=NNO_3$	(256)
$C_6H_5NHCOCH_3$	N_2O_4	$C_6H_5N=NNO_2$, CH_3COOH	(244)
O_2N—⟨ ⟩—NH_2	N_2O_4	O_2N—⟨ ⟩—$N=NNH$—⟨ ⟩—NO_2, O_2N—⟨ ⟩—$N=NNO_3$	(91)
(2-nitroaniline) NH_2 with NO_2	N_2O_4	$N=NNH$ structures, $N=NNO_3$	(91)
O_2N—⟨ ⟩—NH_2	N_2O_4	O_2N—⟨ ⟩—$N=NNH$—⟨ ⟩—NO_2, O_2N—⟨ ⟩—$N=NNO_3$	(91)
O_2N—⟨ ⟩—$NHCH_3$	N_2O_3	O_2N—⟨ ⟩—NCH_3 with $N=O$	(211)
(with NO_2) O_2N—⟨ ⟩—$NHCH_3$	N_2O_3	O_2N—⟨ ⟩—NCH_3 with $N=O$ and NO_2	(211)
O_2N—⟨ ⟩—NHC_2H_5	N_2O_3	O_2N—⟨ ⟩—NC_2H_5 with $N=O$	(211)

TABLE 7—*Continued*

COMPOUND	OXIDE OF NITROGEN	PRODUCTS FORMED	REFERENCE
O_2N—(ring, Cl)—$NHCH_3$	N_2O_3	O_2N—(ring, Cl)—$N(CH_3)$, $N=O$	(211)
O_2N—(ring, Cl)—$NHCH_3$	N_2O_3	O_2N—(ring, Cl)—$N(CH_3)$, $N=O$	(211)
$CH_3\overset{NOH}{C}CH_3$	N_2O_3 or N_2O_4	$CH_3\underset{NO_2}{\overset{NO}{C}}CH_3$	(196)
$C_2H_5\overset{NOH}{C}CH_3$	N_2O_3 or N_2O_4	$C_2H_5\underset{NO_2}{\overset{NO}{C}}CH_3$	(196)
$C_2H_5\overset{NOH}{C}C_2H_5$	N_2O_3 or N_2O_4	$C_2H_5\underset{NO_2}{\overset{NO}{C}}C_2H_5$	(196)
$CH_3CO\overset{CH_3}{C}HCOOC_2H_5$	N_2O_3	$O=NC\overset{CH_3}{H}COOC_2H_5$ (unstable)	(194)
$CH_3CO\overset{C_2H_5}{C}HCOOC_2H_5$	N_2O_3	$O=NC\overset{C_2H_5}{H}COOC_2H_5$ (unstable)	(194)
$CH_3CO\overset{C_4H_9}{C}HCOOC_2H_5$	N_2O_3	$O=NC\overset{C_2H_5}{H}COOC_2H_5$ (unstable)	(194)
$CH_2CO\underset{CH_2COOC_2H_5}{C}HCOOC_2H_5$	N_2O_3	$O=NC\underset{CH_2COOC_2H_5}{H}COOC_2H_5$ (unstable)	(191, 193, 194)
$CH_3CO\underset{CH_3COCHCOOC_2H_5}{C}HCOOC_2H_5$	N_2O_3	$O=NC\underset{CH_3COCHCOOC_2H_5}{H}COOC_2H_5$ (unstable)	(194)

TABLE 7—*Continued*

COMPOUND	OXIDE OF NITROGEN	PRODUCTS FORMED	REFER-ENCE
CHO | $CH_3CHCOOC_2H_5$	N_2O_3	N=O | $CH_3CHCOOC_2H_5$ (unstable)	(191)
COCH₃ | $C_3H_7CHCOOC_2H_5$	N_2O_3	N=O | $C_3H_7CHCOOC_2H_5$ (unstable)	(191)
$C_6H_5COCH(COOC_2H_5)_2$	N_2O_3	$O=NCH(COOC_2H_5)_2$ (unstable)	(191)
$(CH_3)_2CHCH_2COOC_2H_5$	N_2O_3	N=O | $(CH_3)_2CHCHCOOC_2H_5$ (unstable)	(192)
CN | $C_6H_5CC_6H_5$ $C_6H_5CC_6H_5$ | CN	N_2O_4	$(C_6H_5)_2C(NO_2)CN$ or $(C_6H_5)_2C(ONO)CN$	(257)
	N_2O_3		(179)
	N_2O_4		(260)

nitroso compounds would form from nitrogen trioxide with compounds of the type

$$\begin{array}{c} H \\ | \\ R{-}C{-}COOC_2H_5 \\ | \\ R' \end{array}$$
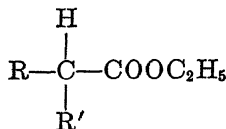
when R' was H, $CH_3C\diagdown^{\displaystyle O}$, $C_6H_5C\diagdown^{\displaystyle O}$, alkyl, or —COOH.

Instances are recorded showing that nitrogen oxides are capable of transforming geometric isomers from one form to the other. Thus Schmidt (180) was able partially to convert maleic to fumaric acid. Meyer (118) and Gottlieb (76) transformed oleic to elaidic acid.

One example is recorded in which a six-membered ring compound was changed to a five-membered ring compound (179). 1,4-Naphthoquinone reacted with nitrogen trioxide to produce I, which Schmidt named α,γ-diketohydrindene nitrosite.

I   II   III
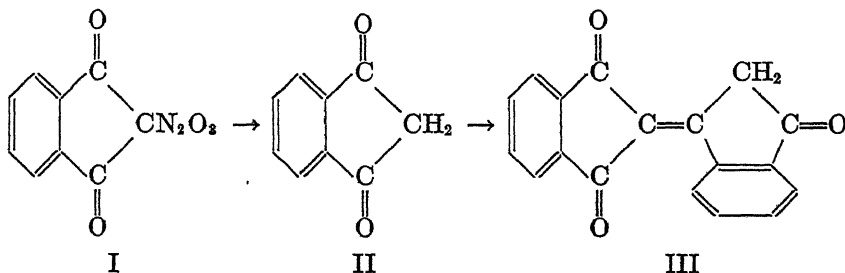
Compound I was relatively unstable and in hot water lost oxides of nitrogen to form diketohydrindene (II), which in turn gradually changed to the anhydro-bisdiketohydrindene (III).

Masson (113) allowed nitrogen trioxide to react with glycerol. An unstable compound was formed to which was assigned the formula $C_3H_5(NO_2)_3$. The analytical data were not convincing. It was believed to be a nitrous ester.

Wittig (257) studied one example in which a saturated molecule was split by nitrogen tetroxide. The dinitrile of tetraphenylsuccinic acid in chloroform treated with nitrogen tetroxide gave IV or V in better than 50 per cent yield.

IV   V   VI
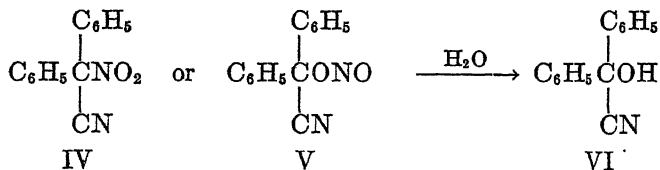
The product hydrolyzed with water and acetic acid to produce the cyanohydrin VI, thus suggesting that structure V is to be preferred.

IX. SUMMARY

With the availability of inexpensive nitrogen tetroxide this area of research should be greatly stimulated. It would seem probable that nitrations with nitrogen tetroxide would be limited to special cases in which it might offer a peculiar advantage. The most fruitful fields of research are likely to be found in the use of nitrogen tetroxide as an oxidizing agent and in addition to compounds containing multiple bonds. The latter field is especially attractive, since the addition compounds may be reduced to amines or aminoalcohols, some of which should be useful. The reduction of these compounds has often been unfortunate because of the low yields obtained. But with the techniques now available for small- or large-scale reductions it may be possible to overcome this difficulty.

Many of the experiments which have been done with nitrogen tetroxide should be repeated under conditions controlled as accurately as possible. In those experiments in which solvents are used, a variety of solvents should be tried, because the medium in which these reactions take place often exerts a profound influence. It is possible that some inert gas could often be added with advantage when vapor-phase reactions are tried.

REFERENCES

(1) ABDERHALDEN, E., AND HEYNS, K.: Ber. 67, 530–47 (1934).

(2) ALEXANDER, P.: Z. angew. Chem. 20, 1355–67 (1907).

(3) ALEXANDER, P.: Z. angew. Chem. 24, 680 (1911).

(4) ALLEN, C. F. H., ELIOT, C. G., AND BELL, A.: Can. J. Research 17B, 75–88 (1939); Chem. Abstracts 33, 6284 (1939).

(5) ANGELI, A.: Ber. 24, 3994–6 (1891).

(6) ANGELI, A.: Ber. 25, 1956–63 (1892).

(7) ARGO, W. L., JAMES, E. M., AND DONNELLY, J. L.: J. Phys. Chem. 23, 578–85 (1919).

(8) AVANESOV, D., AND VYATSKIN, I.: Khim. Referat. Zhur. 2, No. 5, 43 (1939); Chem. Abstracts 34, 2262 (1940).

(9) BAILEY, R.: U. S. patent 1,319,748 (October 28, 1919).

(10) BAKER, H. B., AND BAKER, M.: J. Chem. Soc. 102, 2339 (1912); Chem. Abstracts 7, 1332 (1913).

(11) BAMBERGER, E.: Ber. 30, 506–13 (1897).

(12) BAMBERGER, E., AND MÜLLER, J.: Ber. 32, 3546–54 (1899).

(13) BAMBERGER, E , AND PEMSEL, W.: Ber. 36, 57–84 (1903).

(14) BARNETT, E.: J. Chem. Soc. 127, 2040–4 (1925).

(15) BASS, L., AND JOHNSON, T. B.: J. Am. Chem. Soc. 46, 456–61 (1924).

(16) BATTLEGAY, M., AND KERN, W.: Bull. soc. chim. 41, 1336–41 (1927); Chem. Abstracts 22, 923 (1928); Brit. Chem. Abstracts 1928A, 34.

(17) BATTLEGAY, M., AND RASUMEJEW, A.: British patent 262,097; French patent 619,224.

(18) BIBB, C. H.: Ind. Eng. Chem. 24, 10–12 (1932).

(19) BILTZ, H.: Ber. 30, 1201–10 (1897).

(20) BILTZ, H.: Ber. 35, 1528–33 (1902).

(21) BOGDANOV, M. I.: Anilinokrasochnaya Prom. **3**, 133–44 (1933); Chem. Abstracts **27**, 5312 (1933).

(22) BORN, G.: Ber. **29**, 90–102 (1896).

(23) BOUVEAULT, L., AND WAHL, A.: Compt. rend **137**, 196 (1903).

(24) BOUVEAULT, L., AND WAHL, A.: Compt. rend. **138**, 1221-3 (1904); Chem. Zentr. **1904**, II, 27.

(25) BOUVEAULT, L., AND WAHL, A.: Bull. soc. chim. **31**, 679–82 (1904); Chem. Zentr. **1904**, II, 195.

(26) BURROWS, R. B., AND HUNTER, L.: J. Chem. Soc. **134**, 1357–60 (1932).

(27) CAHOURS, A.: Ann. **41**, 76 (1842).

(28) CIUSA, R., AND PESTALOZZA, U.: Atti accad. Lincei **17**, i, 840 (1908); Chem. Zentr. **1908**, II, 945.

(29) CIUSA, R., AND PESTALOZZA, U.: Atti accad. Lincei **17**, i, 840 (1908); Chem. Abstracts **3**, 1168 (1909).

(30) CIUSA,.R., AND PESTALOZZA, U.: Gazz. chim. ital. [I] **39**, 304–11 (1909); Chem. Abstracts **3**, 1531 (1909).

(31) COHEN, B., AND CALVERT, H. I.: J. Chem. Soc. **71**, 1050-7 (1897).

(32) COHEN, B., AND HARRISON, W. H.: J. Chem. Soc. **71**, 1057-9 (1897).

(33) CONRAD, M., BISCHOFF, C. A., AND GUTHZEIT, M.: Ann. **209**, 211–18 (1881).

(34) CURTISS, R. S.: Am. Chem. J. **33**, 603–4 (1905).

(35) CURTISS, R. S.: Am. Chem. J. **35**, 477–86 (1906).

(36) CURTISS, R. S., AND KOSTALEK, J. A.: J. Am. Chem. Soc. **33**, 962–74 (1911).

(37) DEM'YANOV, N. YA.: J. Russ. Phys. Chem. Soc. **33**, 283–9 (1901); Brit. Chem. Abstracts **1901**, I, 554.

(38) DEM'YANOV, N. YA., AND SIDORENKO, K. W.: J. Russ. Phys. Chem. Soc. **41**, 832 (1908); Brit. Chem. Abstracts **1909**, I, 754.

(39) DEM'YANOV, N. YA.: Ann. inst. agron. Moscow **4**, Heft 4, 155–217 (1898); Chem. Zentr. **1899**, I, 1064.

(40) DEM'YANOV, N. YA.: Ber. **40**, 245–6 (1907).

(41) DEM'YANOV, N. YA.: J. Russ. Phys. Chem. Soc. **36**, 15 (1904).

(42) DEM'YANOV, N. YA.: Anilinokrasochnaya Prom. **4**, 132–43 (1934); Chem. Abstracts **28**, 5401 (1934).

(43) DEM'YANOV, N. YA., AND IVANOV, A. A.: Comp. rend. acad. sci. (U. R. S. S.) [N.S.] **1**, 318–24 (1934); Chem. Abstracts **28**, 4374 (1934).

(44) DEM'YANOV, N. YA., AND WILLIAMS, V. V.: Bull. acad. sci. U.R.S.S., Classe sci. math. nat. **1931**, 1123–40; Chem. Abstracts **26**, 3238 (1932).

(45) DENNSTEDT, M., AND AHRENS, C.: Ber. **28**, 1331-5 (1895).

(46) DIELS, OTTO: Ann. **432**, 1–45 (1923).

(47) DULOW, R.: Bull. inst. pin **1934**, 129–39; Chem. Abstracts **28**, 7255 (1934).

(48) EGOROFF, I. W.: J. Russ. Phys. Chem. Soc. **35**, 358–75 (1903); Brit. Chem. Abstracts **1903**, I, 789.

(49) EGOROFF, I W.: J. Russ. Phys. Chem. Soc. **35**, 466–82 (1903); Brit. Chem. Abstracts **1903**, I, 790.

(50) EGOROFF, I. W.: J. Russ. Phys. Chem. Soc. **35**, 482-8 (1903); Brit. Chem. Abstracts **1903**, I, 790.

(51) EGOROFF, I. W.: J. Russ. Phys. Chem. Soc. **35**, 965–73 (1903); Brit. Chem. Abstracts **1904**, I, 216.

(52) EGOROFF, I. W.: J. Russ. Phys. Chem. Soc. **35**, 973–97 (1903); Brit. Chem. Abstracts **1904**, I, 217.

(53) EGOROVA, O. I.: Ukraïn. Khem. Zhur. **4**, Sci. Pt., 193-8 (1929); Chem. Abstracts **24**, 1078 (1930).

(54) EGOROV, O. I.: J. Russ. Phys. Chem. Soc. **62**, 1097–1100 (1930); Chem. Abstracts **25**, 2706 (1930).

(55) EMDEN, F.: Ber. **58**, 2522 (1925).

(56) ERDMANN, H.: Ber. **24**, 2771–5 (1891).
(57) FILIPPUICHEV, S. F., AND PETROV, P. P.: Anilinokrasochnaya Prom. **3**, 351–3; Chem. Abstracts **28**, 3720 (1934).
(58) FORSTER, M. O., AND MICKLETHWAIT, F. M.: J. Chem. Soc. **79**, 325–35 (1904).
(59) FORSTER, M O., AND MICKLETHWAIT, F. M.: Proc. Chem. Soc **20**, 19–20 (1904); Chem. Zentr **1904**, I, 807.
(60) FRANKLAND, P. F., AND FARMER, R. C.: J. Chem. Soc. **79**, 1356–73 (1901).
(61) FRANKLIN AND WILKENS: British patent 532,686 (1940).
(62) French patent 709,823; Chem. Abstracts **26**, 1302 (1932).
(63) FRIEDBURG, L. H., AND MANDEL, J. A.: J. Am. Chem. Soc. **12**, 7–12 (1890).
(64) FRIEDBURG, L. H., AND MANDEL, J. A.: J. Am. Chem. Soc. **12**, 7–12 (1890); Chem. Zentr. **1890**, II, 8.
(65) FROLICH, PER K., HARRINGTON, P. J., AND WAITT, A. H.· J. Am. Chem. Soc. **50**, 3216–21 (1928).
(66) GABRIEL, S.: Ber. **18**, 1251 (1885).
(67) GABRIEL, S.· Ber. **18**, 2436–42 (1885).
(68) GENVRESSE, P.: Compt. rend. **130**, 918–20 (1900); Chem. Zentr. **1900**, I, 1021.
(69) German patent 207,180 (February 2, 1908); Chem. Abstracts **3**, 1935 (1909).
(70) German patent 214,045.
(71) German patents 215,335; 234,289; 254,710; 256,623; 268,049.
(72) GIACALONE, A.: Gazz. chim. ital **61**, 828–32 (1931); Chem. Abstracts **26**, 1910 (1932).
(73) GILMAN, E., AND JOHNSON, T. B.: J. Am. Chem. Soc. **50**, 3341–8 (1928).
(74) GILMAN, H.: *Organic Syntheses*, Collective Vol. I, p. 261. John Wiley and Sons, Inc., New York (1932).
(75) GORGAS, A.: Ber. **63B**, 2700–5 (1930).
(76) GOTTLIEB, J.: Ann. **57**, 52 (1846).
(77) GRÄNACHER, CH., AND SCHAUFELBERGER, P.: Helv. Chim. Acta **3**, 721–37 (1920); Chem. Abstracts **15**, 668 (1920).
(78) GRÄNACHER, CH., AND SCHAUFELBERGER, P.: Helv. Chim. Acta **5**, 392–5 (1922); Chem. Abstracts **17**, 2864 (1923).
(79) GUTHRIE, F. Ann. **119**, 83–92 (1861).
(80) GUTHRIE, F. Ann. **121**, 117 (1862).
(81) HARRIES, C. Ber. **34**, 2991 (1901).
(82) HARRIES, C. Ber. **35**, 3256 (1902).
(83) HARRIES, C. Ber. **38**, 87–90 (1905).
(84) HARRIES, C. Z. angew. Chem. **20**, 1265–71 (1907).
(85) HARRIES, C. Z. angew. Chem. **20**, 1969 (1907); Chem. Abstracts **2**, 714 (1908).
(86) HASS, H. B., DORSKY, J., AND HODGE, E. B.: Ind. Eng. Chem. **33**, 1138–43 (1941).
(87) HASS, H. B., AND HODGE, E. B.: Canadian patent 382,346 (June 27, 1939); Chem. Abstracts **33**, 6881 (1939).
(88) HASS, H. B., AND RILEY, E. F.: Chem. Rev. **32**, 373–430 (1943).
(88a) HENDRICKS, S. B.: Z. Physik **70**, 699 (1931).
(89) HENRY, L.: Ber. **2**, 279 (1869).
(90) HENRY, L.: Bull. sci. acad. roy. Belg. [2] **38**, 1 (1874).
(91) HOUSTON, B., AND JOHNSON, T. B.: J. Am. Chem. Soc. **47**, 3011–18 (1925).
(92) IL'INSKII, M., MAKSOROV, B. V., AND ELAGIN, N. V.: J. Chem. Ind. (Moscow) **5**, 469–73 (1928); Chem. Abstrcts **22**, 3888 (1928).
(93) IPATIEFF, W., AND SSOLONIMA, A.: J. Russ. Phys. Chem. Soc. **33**, 496–501 (1901); Chem. Zentr. **1901**, II, 1201.
(94) JOHNSON, K. (to Commercial Solvents Corporation): U. S. patent 2,213,444 (September 3, 1940); Chem. Abstracts **35**, 465 (1941).
(95) KLINGSTEDT, F. W.: Ber. **58**, 2363–70 (1925).
(96) KOLBE, H.: Ber. **2**, 326 (1869).
(97) KUNZ, J.: Ber. **31**, 1528–31 (1898).

(98) LaTowsky, L., MacQuiddy, E., and Tollman, P.: J. Ind. Hyg. Toxicol. **23**, 129–33 (1941); Chem. Abstracts **35**, 7575 (1941).

(99) Lauer, K., and Atarashi, K.: Ber. **68B**, 1373–6 (1935).

(100) Leeds, A.: J. Am. Chem. Soc. **2**, 277–87 (1880).

(101) Leeds, A.: Ber. **13**, 1993 (1880).

(102) Leeds, A.: Ber. **14**, 482–5 (1881).

(103) Lehmann, K. B., and Hasegawa: Arch. Hyg. **77**, 311–23 (1913); Chem. Abstracts **7**, 2432 (1913).

(104) Leupold, E.: Ber. **34**, 2829–37 (1901).

(105) Lidoff, P. H.: J. Russ. Phys. Chem. Soc. **29**, 214–15 (1897); Chem. Zentr. **1897**, II, 445.

(106) Liebermann, C., and Lindemann, L.: Ber. **13**, 1584–9 (1880).

(107) Lipp, P.: Ann. **399**, 241–60 (1913).

(108) Lunge, G.: Ber. **11**, 1641 (1878).

(109) McKee, R., and Wilhelm, R.: Ind. Eng. Chem. **28**, 662–7 (1936).

(110) Makarova, L. G., and Nesmeyanov, A. N.: J. Gen. Chem. (U.S.S.R.) **9**, 771–9 (1939); Chem. Abstracts **34**, 391 (1940).

(111) Marshall, J.: U. S. patent 1,473,825 (October 5, 1921).

(112) Maslov, N. J.: J. Gen. Chem. (U.S.S.R.) **10**, 1915–17 (1940); Brit. Chem. Abstracts **1941**, II, 311.

(113) Masson, O.: Chem. News **47**, 278 (1883); Chem. Zentr. **1883**, 484; J. Chem. Soc. **43**, 348 (1883).

(114) Maurer, K., and Drefahl, G.: Ber. **75B**, 1489–91 (1942).

(115) Maurer, K., and Reiff, G.: J. Makromal, Chem. **1**, 27–34 (1943); Chem. Abstracts **38**, 1211 (1944).

(116) Meisenheimer, J., and Connerade, E.: Ann. **330**, 133–84 (1903).

(117) Mellor, J. W.: *A Comprehensive Treatise on Inorganic and Theoretical Chemistry*, Vol. VIII, pp. 529–48. Longmans, Green and Company, London (1928).

(118) Meyer, H.: Ann. **35**, 174–88 (1840).

(119) Meyer, V.: Ann. **171**, 1–64 (1876).

(120) Meyer, V.: Ber. **21**, 1291–5 (1888).

(121) Michael, A., and Carlson, G. H.: J. Am. Chem. Soc. **59**, 843–9 (1937).

(122) Michael, A., and Carlson, G. H.: J. Org. Chem. **4**, 169–97 (1939).

(123) Michael, A., and Carlson, G. H.: J. Org. Chem. **5**, 1–13 (1940).

(124) Michael, A., and Carlson, G. H.: J. Org. Chem. **5**, 14–23 (1940).

(125) Miller, A. K.: Chem. News **56**, 206 (1887); Chem. Zentr. **1887**, 58, 1487.

(126) Monti, L.: Gazz. chim. ital. **60**, 787–97 (1930); Chem. Abstracts **25**, 1483 (1931).

(127) Monti, L., Martello, V., and Valente, F.: Gazz. chim. ital. **66**, 31–8 (1936); Chem. Abstracts **30**, 6359 (1936).

(128) Neber, P. W., and Paeschke, S.: Ber. **59**, 2140–50 (1926).

(129) Onishchenko, A. S.: Bull. acad. sci. U.R.S.S., Classe sci. math. nat., Sér. chim. **1937**, 209–23; Chem. Abstracts **31**, 5341 (1927).

(130) Onischenko, A. S.: Bull. acad. sci. U.R.S.S., Classe sci. math. nat., Sér. chim. **1937**, 539–46; Chem. Abstracts **32**, 2089 (1938).

(130a) Palmer, W. G.: *Valency*, pp. 47, 78, 127, 190. Cambridge University Press, London (1944).

(131) Pinck, L. A.: J. Am. Chem. Soc. **49**, 2536–9 (1927).

(132) Pinck, L. A.: Ind. Eng. Chem. **22**, 1241–3 (1930).

(133) Ponzio, G.: Gazz. chim. ital. **27**, I, 171–9 (1897); Chem. Zentr. **1897**, I, 857.

(134) Ponzio, G.: J. prakt. Chem. [ii] **62**, 543–4 (1900); Brit. Chem. Abstracts **80**, I, 154 (1901).

(135) Ponzio, G.: Gazz. chim. ital. **31**, I, 262–4 (1901); Chem. Zentr. **1901**, I, 1319.

(136) Ponzio, G.: Gazz. chim. ital. **31**, II, 133–8 (1901); Chem. Zentr. **1901**, II, 1007.

(137) Ponzio, G.: Gazz. chim. ital. **33**, I, 508–12 (1903); Chem. Zentr. **1903**, II, 937.

(138) Ponzio, G.: J. prakt. Chem. [2] **73**, 494–6 (1906); Chem. Zentr. **1906**, II, 328.

(139) PONZIO, G.: Atti accad. Lincei Roma [5] **15**, II, 42–5 (1906); Chem. Zentr. **1906**, II, 951.

(140) PONZIO, G.: Atti accad. Lincei Roma [5] **15**, II, 118–28 (1906); Chem. Zentr. **1906**, II, 1003.

(141) PONZIO, G.: Gazz. chim. ital. **36**, 287–98 (1906); Chem. Zentr. **1906**, II, 1607.

(142) PONZIO, G.: Gazzetta **39i**, 324–6 (1909); Brit. Chem. Abstracts **1909A**, I, 308; Chem. Abstracts **3**, 1531 (1909).

(143) PONZIO, G., AND DE GASPARI, A.: Gazz. chim. ital. **28**, II, 269–79 (1898); Chem. Zentr. **1898**, II, 965.

(144) POSNER, T., AND ASCHERMANN, G.: Ber. **53**, 1925–40 (1920).

(145) POSNER, T., AND HEUMANN, W.: Ber. **56**, 1621–9 (1923).

(146) PRIEBS, B.: Ann. **225**, 319–64 (1884).

(147) PURANEN, N.: Ann. Acad. Sci. Fennicae **37A**, No. 10, 80 pp. (1933); Chem. Abstracts **27**, 5062 (1933).

(148) PURGOTTI, A.: Ann. ist. super. agrar. Portici [3] **3**, 41–6 (1929); Chem. Abstracts **25**, 3632 (1931).

(149) RASOWMEEFF, A.: British patent 262,097 (November 24, 1925); Chem. Abstracts **21**, 3626 (1927).

(150) RIEBSOMER, J., AND HAGER, G.: Unpublished research.

(151) RIEBSOMER, J., AND REINECKE, R.: Unpublished research.

(152) RODIONOV, V. M., AND OBLITZEVA, T. A.: Trans. VI Mendeleev Congr. Theoret. Applied Chem. 1932, **2**, Pt. 1, 1002–3 (1935); Chem. Abstracts **30**, 4149 (1936).

(153) RODIONOV, V. M., AND OBLITZEVA, T. A.: Trudy VI Vsesoyuz. Mendeleev. S'ezda Teoret. i Priklad. Chim. **2**, No. 1, 1002–3 (1938); Chem. Abstracts **34**, 6572 (1940).

(154) RUGGERI, G.: Atti accad. sci. Toreno **58**, 441 (1923); Gazz. chim. ital. **53**, 691–8 (1923); Chem. Abstracts **18**, 227 (1924).

(155) RULE, A.: J. Chem. Soc. **93**, 1560–4 (1908).

(156) RYAN, H., AND CONNALLY, A.: Sci. Proc. Roy. Dublin Soc. **17**, 125–30 (1923); Chem. Abstracts **17**, 1792 (1923).

(157) RYAN, H., AND CULLINANE, N.: Sci. Proc. Roy. Dublin Soc. **17**, 119–24 (1923); Chem. Abstracts **17**, 1792 (1923).

(158) RYAN, H., AND CULLINANE, N.: Sci. Proc. Roy. Dublin Soc. **17**, 321–6 (1924); Chem. Abstracts **18**, 1655 (1924).

(159) RYAN, H., AND DONNELLAN, A.: Sci. Proc. Roy. Dublin Soc. **17**, 113–8 (1923); Chem. Abstracts **17**, 1791 (1923).

(160) RYAN, H., AND DRUMM, P.: Sci. Proc. Roy. Dublin Soc. **17**, 313–20 (1924); Brit. Chem. Abstracts **1924A**, I, 504.

(161) RYAN, H., AND EGAN, M.: Proc. Roy. Irish Acad. **36B**, 329–33 (1924).

(162) RYAN, H., AND GLYNN, M.: Proc. Roy. Irish Acad. **37B**, 78–83 (1926); Chem. Abstracts **20**, 2834 (1926).

(163) RYAN, H., AND KEANE, J.: Sci. Proc. Roy. Dublin Soc. **17**, 287–95 (1924).

(164) RYAN, H., AND KEANE, J.: Sci. Proc. Roy. Dublin Soc. **17**, 297–303 (1924).

(165) RYAN, H., AND KENNEY, T.: Sci. Proc. Roy. Dublin Soc. **17**, 305–11 (1924); Brit. Chem. Abstracts **1924A**, I, 505.

(166) RYAN, H., AND MARKEY, A.: Proc. Roy. Irish Acad. **37B**, 71–7 (1926); Chem. Abstracts **20**, 2834 (1926).

(167) RYAN, H., AND O'DONOVAN, J. L.: Sci. Proc. Roy. Dublin Soc. **17**, 131–7 (1923); Chem. Abstracts **17**, 1792 (1923).

(168) RYAN, H., AND O'TOOLE, P. K.: Sci. Proc. Roy. Dublin Soc. **17**, 139–55 (1923); Chem. Abstracts **17**, 1792 (1923).

(169) SAN FOURCHE, A., AND BUREAU, J.: Compt. rend. **202**, 66–8 (1936).

(170) SCHAARSCHMIDT, A.: Ber. **57**, 2065–72 (1924).

(171) SCHAARSCHMIDT, A.: Z. angew. Chem. **37**, 933–8 (1924); Chem. Abstracts **19**, 942 (1925).

(172) SCHAARSCHMIDT, A.: Z. angew. Chem. **39**, 1457–9 (1926); Chem. Abstracts **21**, 3055 (1927).

(173) SCHAARSCHMIDT, A., BALZERKIEWICZ, H., AND GANTE, J.: Ber. **58**, 499–502 (1925).
(174) SCHAARSCHMIDT, A., AND HOFMEIER, H.: Ber. **58**, 1047–54 (1925).
(175) SCHAARSCHMIDT, A., AND SMOLLE, E.: Ber. **57**, 32–42 (1924)
(176) SCHAARSCHMIDT, A., VEIDT, M., AND SCHLOSSER, F.. Ber. **55**, 1103–12 (1922).
(177) SCHALL, R.: Ber. **16**, 1897–1903 (1883).
(178) SCHLENK, W.: Ann. **394**, 178–223 (1912).
(179) SCHMIDT, J.: Ber. **33**, 543–7 (1900).
(180) SCHMIDT, J.: Ber. **33**, 3241(1900).
(181) SCHMIDT, J : Ber. **33**, 3251 (1900).
(182) SCHMIDT, J.: Ber. **34**, 619 (1901).
(183) SCHMIDT, J.: Ber. **34**, 623 (1901).
(184) SCHMIDT, J.: Ber. **34**, 3536–43 (1901).
(185) SCHMIDT, J.: Ber. **35**, 2323 (1902).
(186) SCHMIDT, J.: Ber. **35**, 2336 (1902).
(187) SCHMIDT, J.: Ber. **35**, 3721–40 (1902).
(188) SCHMIDT, J.: German patent 126,798; Brit. Chem. Abstracts **82**, I, 500 (1902).
(189) SCHMIDT, J.: Ber. **36**, 1768 (1903).
(190) SCHMIDT, J : Ber. **36**, 1775 (1903).
(191) SCHMIDT, J., AND DIETERLE, H.: Ann. **377**, 30–70 (1910).
(192) SCHMIDT, J., AND HAID, A.: Ann. **377**, 23–30 (1910).
(193) SCHMIDT, J., AND WIDMAN, K.: Ber. **42**, 497 (1909).
(194) SCHMIDT, J., AND WIDMAN, K.: Ber. **42**, 1886 (1909).
(195) SCHMITT, CH.: Compt. rend. **140**, 1400–1 (1905); Chem Zentr. **1905**, II, 120.
(196) SCHOLL, R.: Ber. **21**, 506–10 (1888).
(197) SCHOLL, R.: Ber. **23**, 3490–3505 (1890).
(198) SEMENOFF, A.: Jahresber. **1864**, 480; Z. Chem. Pharm., p. 129 (1864); Phil. Mag. [4] **29**, 306 (1865).
(199) SHORYGIN, P. P., AND KHAIT, E. V.: J. Gen. Chem. (U.S.S.R.) **7**, 188–92 (1937).
(200) SHORYGIN, P. P., AND TOPCHIEV, A.: Ber. **67**, 1362–8 (1934).
(201) SHORYGIN, P. P., AND TOPCHIEV, A.: J. Gen. Chem. (U.S.S.R.) **5**, 549–54 (1935); Brit. Chem. Abstracts **1936A**, 61.
(202) SHORYGIN, P. P., AND TOPCHIEV, A : Ber. **69B**, 1874–7 (1936).
(203) SHORYGIN, P. P., TOPCHIEV, A. V., AND ANAN'INA, V. A.: J. Gen. Chem.(U.S.S.R.) **8**, 981–90 (1938); Chem. Abstracts **33**, 3781 (1939).
(204) SHILOV, E. A.: J. Russ. Phys. Chem. Soc. **62**, 65–9 (1930); Chem. Abstracts **24**, 4289 (1930).
(205) SIDGWICK, N. V.: *Organic Chemistry of Nitrogen*, pp. 225–6. Oxford University Press, London (1937).
(206) SIDORENKO, K.: J. Russ. Phys. Chem. Soc. **36**, 898–905 (1904); Chem. Zentr. **1904**, II, 1024.
(207) SIDORENKO, K.: J. Russ. Phys. Chem. Soc **38**, 955–8 (1906); Chem. Zentr. **1907**, I, 399.
(208) SIDORENKO, K.: J. Russ. Phys. Chem. Soc. **45**, 1585–1604 (1913); Chem. Abstracts **8**, 493 (1914).
(209) SMITH, L. I., AND TAYLOR, L. F.: J. Am. Chem. Soc. **57**, 2460–3 (1935).
(210) SOMMER, E.: Ber. **29**, 356–60 (1896).
(211) STOERMER, R.: Ber. **31**, 2523–41 (1898).
(212) STRAUS, F., AND EKHARD, W.: Ann. **444**, 146–64 (1925).
(213) THORPE, J. F , AND FARMER, E. H.: *The Science of Petroleum*, Vol. II, pp. 936–84. Oxford University Press, London (1938).
(214) TILDEN, W. A., AND SUDBOROUGH, J. J.: J. Chem. Soc. **63**, 479–84 (1893); Chem. Zentr. **1893**, I, 635.
(215) TITOV, A. I.: J. Gen. Chem. (U.S.S.R) **7**, 591–4 (1937); Chem. Abstracts **31**, 5773 (1937).
(216) TITOV, A. I.: J. Gen. Chem. (U.S.S.R.) **7**, 1695–1903 (1937); Chem. Abstracts **31**, 8516 (1937).

(217) TITOV, A. I.: J. Gen. Chem. (U.S.S.R.) **10**, 1878–84 (1940); Chem. Abstracts **35**, 4356 (1941).

(218) TITOV, A. I., AND BARYSHNIKOVA, A. N.: J. Gen. Chem. (U.S.S R.) **6**, 1801, 1855 (1936); Chem. Abstracts **31**, 4285 (1937).

(219) TOENNIES, P.: Ber. **20**, 2982–7 (1887).

(220) UNRUH, C., AND KENYON, W.: J. Am. Chem. Soc. **64**, 127–31 (1942).

(221) URBÁNSKI, T., AND SŁOŃ, M.: Compt. rend **203**, 620–2 (1936); Chem. Abstracts **31**, 654 (1937).

(222) URBÁNSKI, T., AND SŁOŃ, M.: Compt. rend **204**, 870–1 (1937); Chem Abstracts **31**, 3868 (1937).

(223) URBÁNSKI, T., AND SŁOŃ, M.: Róczniki Chem. **16**, No. 4–5, 466–9 (1936); Chem. Abstracts **31**, 6190 (1937).

(224) URBÁNSKI, T., AND SŁOŃ, M.: Roczniki Chem. **17**, 161–4 (1937); Chem. Abstracts **31**, 6190 (1937).

(225) URBÁNSKI, T., AND SŁOŃ, M.: Przeglad Chem. **2**, 42–3 (1938); Chem. Abstracts **32**, 42–3 (1939).

(226) URBÁNSKI, T., AND SŁOŃ, M.: IIᵉ Congr. mondial pétrole **2**, Sect. 2, Phys., chim., raffinage, 163–7 (1937); Chem. Abstracts **33**, 532 (1939).

(227) VARMA, S. V., AND KRISHNAMURTHY, P. V.: Quart. J. Indian Chem. Soc. **3**, 323–7 (1926); Chem. Abstracts **21**, 2256 (1927).

(228) WALLACH, O.: Ann. **239**, 1–54 (1887).

(229) WALLACH, O.: Ann. **241**, 288–315 (1887).

(230) WALLACH, O.: Ann. **241**, 315 (1887).

(231) WALLACH, O.: Ann. **248**, 161–74 (1888).

(232) WALLACH, O.: Ann. **262**, 324 (1891).

(233) WALLACH, O.: Ann. **332**, 305–51 (1904).

(234) WEBER, C.: Ber. **35**, 1947–51 (1902).

(235) WEBER, C.: Ber. **36**, 3103–8 (1903).

(236) WIELAND, H.: Ann. **328**, 154–255 (1903).

(237) WIELAND, H.: Ann. **329**, 225–68 (1903).

(238) WIELAND, H.: Ber. **36**, 2315–19 (1903).

(239) WIELAND, H.: Ber. **36**, 2558–68 (1903).

(240) WIELAND, H.: Ber. **36**, 3020 (1903).

(241) WIELAND, H.: Ber. **53**, 1343–6 (1920).

(242) WIELAND, H.: Ann. **424**, 71 (1921).

(243) WIELAND, H., *et al.*: Ann. **424**, 75–92 (1921).

(244) WIELAND, H.: Ber. **54**, 1776–84 (1921).

(245) WIELAND, H., AND BLOCH, S.: Ber. **37**, 1524–36 (1904).

(246) WIELAND, H., AND BLOCH, S.: Ber. **37**, 2524–8 (1904).

(247) WIELAND, H., AND BLOCH, S.: Ann. **340**, 63–85 (1905).

(248) WIELAND, H., AND BLUMICK, E.: Ann. **424**, 100 (1921).

(249) WIELAND, H., AND GAMBARJAN, S.: Ber. **39**, 1499–1506 (1906).

(250) WIELAND, H., AND RAHN, F.: Ber. **54**, 1770–6 (1921).

(251) WIELAND, H., AND REISENEGGER, C.: Ann. **401**, 244–51 (1913).

(252) WIELAND, H., AND ROTH, K.: Ber. **53**, 210–30 (1920).

(253) WIELAND, H., AND SEMPER, L.: Ann. **358**, 36–70 (1908).

(254) WIELAND, H, AND STENZL, H.: Ber. **40**, 4825–34 (1907).

(255) WIELAND, H., AND STENZL, H.: Ann. **360**, 299–322 (1908).

(256) WITT, O. N.: Tageblatt der Natur-forschung-versuchung zu Baden-Baden, p. 194 (1879); Chem. Zentr. **1880**, II, 226.

(257) WITTIG, G., AND POCKELS, U.: Ber. **69B**, 790–2 (1936).

(258) YACKEL, E., AND KENYON, W.: J. Am. Chem. Soc. **64**, 121–7 (1942).

(259) YEGOROV, Y.: J. prakt Chem. **86**, 521–39 (1912); Chem. Abstracts **7**, 1477 (1913).

(260) ZINCKE, TH.: Ann. **435**, 145–73 (1924).

SELENIUM DIOXIDE: PREPARATION, PROPERTIES, AND USE AS OXIDIZING AGENT

G. R. WAITKINS[1] AND C. W. CLARK[2]

Research Laboratories, Canadian Copper Refiners Limited, Montreal East, Quebec, Canada

CONTENTS

I. INTRODUCTION

While the reduction of selenium dioxide and selenites to selenium by various organic compounds was noted by many investigators before 1900, the specific nature of the oxidizing action of selenium dioxide on organic compounds was first indicated in 1930–1932 by Riley (194, 200). Since that time many papers have been published showing the wide application of this reaction to the preparation of new compounds either unobtainable or prepared only with difficulty by other methods from unsaturated hydrocarbons, aldehydes, ketones, heterocyclic nitrogen compounds, terpenes, sterols, fatty oils, and other natural products. This subject has been reviewed in the past by Dupont (62), Hirayama (107),

---

[1] Research Chemist, Canadian Copper Refiners, Ltd.
[2] Director of Research and Development, Canadian Copper Refiners, Limited.

Kratzl (129), Linstead (135), Mayor (150), Melnikov (152), Naves and Igolen (180), Sa (212), Stein (233), and Weygand (255a).

The present, more comprehensive review has been compiled to correlate and to extend the existing literature, in view of the increasing importance of this reagent.

II. PREPARATION OF SELENIUM DIOXIDE

Unlike sulfur, selenium does not support combustion. In the laboratory (11, 98, 119) it is oxidized to selenium dioxide by means of strong oxidizing agents such as nitric acid. The usual procedure (199) is to add commercial selenium powder in small amounts to an excess of concentrated nitric acid. The initial reaction is highly exothermic, and clouds of brown fumes of nitrogen dioxide are evolved. The clear solution of selenious acid is fumed to remove excess nitric acid and then evaporated to dryness to dehydrate selenious acid to selenium dioxide. The crude selenium dioxide obtained in this manner is purified readily by sublimation at 317°C. or above to form glistening, white, monoclinic crystals.

A product of high purity also can be obtained by direct oxidation of selenium with air or oxygen, using traces of nitrogen oxides as catalysts to promote the reaction (59, 92, 161, 178). In this method air or oxygen is bubbled into concentrated nitric acid and then is swept through a glass tube over molten selenium. The selenium dioxide sublimes as it is formed and collects in the cooler end of the tube or in a receiving flask.

Crude selenium dioxide can be prepared commercially by digesting copper refinery slimes containing selenium with sulfuric acid at 400°F. (43). Treadwell and Fränkel (241) have described a process for the manufacture of pure selenium dioxide. According to this patent selenium vapor and excess air are thoroughly mixed, and the preheated gases are conducted through a heated layer of an indifferent porous material such as sand, asbestos, fire-brick, or mixtures of these bodies to effect quantitative conversion of the selenium to selenium dioxide. Selenium dioxide is manufactured currently by an undisclosed process. The commercial product analyzes over 99.9 per cent SeO_2, the remainder being water with the following impurities expressed in parts per million: copper, 0.5; iron, 2; tellurium, 1–2.

The selenium precipitated after reduction of selenium dioxide by various organic compounds can be recovered and converted to selenium dioxide for re-use in some instances with an efficiency of more than 95 per cent, thus making it possible to operate a cyclic oxidizing process economically. The precipitated selenium is collected on a filter and is washed with alcohol or other indifferent solvents. It is then converted to crystalline selenium, if not already in this form, by heat treatment for several hours above 100°C., ground to a fine powder, and rewashed with solvents to remove occluded organic impurities. Selenium containing an appreciable amount of organic impurity may oxidize with explosive violence if heated too strongly with nitric acid (7); therefore, it is preferable in some cases to burn the selenium in air or oxygen, using the methods outlined above.

III. Physical Properties

Selenium dioxide sublimes at 317°C. to form white monoclinic crystals that melt at 340°C. in a sealed tube. The compound has a density of 3.95 at 15°C. and a heat of vaporization of 21,600 cal. per mole. In the vapor state, selenium dioxide shows a greenish yellow color characteristic of selenium dioxide itself and not of free selenium vapor, as is demonstrated by the fact that the color is retained in the presence of free oxygen (262). The relation of vapor pressure to temperature for the equation SeO_2 (s) $\rightarrow SeO_2$ (g) is as follows (102):

t, °C.	20	70	94	124	210	260	311	315
p, mm.	0	12.5	20.2	25.5	54	112.7	610.9	760

IV. Solubility of Selenium Dioxide and Selenious Acid

Of the dioxides of the sulfur group, selenium dioxide is by far the most soluble in water. It absorbs moisture from the air to form solid selenious acid, but even at ordinary temperatures this reaction is reversible and selenious acid effloresces on warm dry days to form selenium dioxide. The dissociation pressures determined by Ishikawa and Abe (112) for the reaction

$$H_2SeO_3 \text{ (s)} \rightarrow SeO_2 \text{ (s)} + H_2O \text{ (g)}$$

illustrate this point:

Temperature, °C.	20	30	40	50	60	70
Pressure of H_2O(g), mm.	0.8	2.0	4.6	10.5	21.2	44.6

According to Julien (119), it is practically impossible to remove the last traces of water from selenium dioxide, since resublimed selenium dioxide that has been desiccated over phosphoric anhydride for a year still retains 0.045–0.088 per cent water. Selenious acid is very soluble in water, as shown by the following data (112) listing the moles of dissolved selenious acid in equilibrium with solid H_2SeO_3 between 20° and 70°C.; above 70°C. the solid phase changes to solid selenium dioxide.

Temperature, °C.	20	30	40	50	60	70
Moles H_2SeO_3 per 100 g. H_2O.	(20)	33.5	44.5	53.7	89.1	176.3

Selenious acid is weaker than sulfurous acid but stronger than the common weak acids such as acetic, benzoic, and carbonic. By the use of the glass electrode Hagisawa (91) estimated the dissociation constants for this dibasic acid to be $K_1 = 2.4 \times 10^{-3}$ and $K_2 = 4.8 \times 10^{-9}$ at 25°C. The molecular structure $HSe(OH)O_2$ has been assigned to selenious acid as the result of magnetic measurements (189).

Selenium dioxide has little or no solubility in organic solvents other than alcohols and related hydroxylic compounds. While it is possible in many cases

solid selenious acid, the customary procedure is to dissolve these substances in a small amount of water and then to add acetic acid, dioxane, alcohol, or other indifferent solvents so as to form a more or less homogeneous solution with the organic compound being oxidized. Selenium dioxide also dissolves in hot 95 per cent sulfuric acid, and such solutions can be used in some instances. Concentrated phosphoric acid dissolves selenium dioxide on warming; at the same time it is a good solvent for many organic compounds and can be used in reactions in which a dehydrating but non-oxidizing medium is desirable (251). In reactions requiring a non-aqueous medium alcoholic solutions of selenium dioxide may be used advantageously.

Alcohols appear to dissolve selenium dioxide at ordinary temperatures by reacting to form alkyl acid selenites according to the equation (6, 101):

$$ROH + SeO_2 \rightleftarrows ROSeO_2H$$
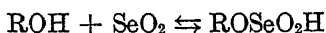
although this is disputed by Prideaux and Green (190). Compounds of this type are obtained as crystalline solids from methanol and ethanol solutions of selenium dioxide by dehydration with calcium chloride in a desiccator. A stronger dehydrating agent such as sulfuric acid causes the alkyl acid selenite to revert to the alcohol and selenium dioxide. These alkyl acid selenites are decomposed easily by water to form the alcohol and selenious acid. Alkyl ammonium selenites result when alcoholic solutions of selenium dioxide are treated with anhydrous ammonia (52). Dialkyl selenite esters, $(RO)_2SeO$, are formed by the reaction of alcohols and selenium dioxide at higher temperatures (153). The lower dialkyl selenite esters are high-boiling liquids that can be distilled under reduced pressure without decomposition. These esters are soluble in the usual organic solvents and, like the alkyl acid selenites, are decomposed readily by water.

de Coninck (45) states that 100 parts of methanol dissolve 10.16 parts of selenium dioxide at 11.8°C. and that 100 parts of 93 per cent ethanol dissolve 6.67 parts of selenium dioxide at 14°C. No other quantitative measurements on the solubility of selenium dioxide in alcohols appear to have been reported in the literature. Qualitative experiments have shown (251) that selenium dioxide can be dissolved in many alcohols readily on warming, in some cases accompanied by slight to considerable reduction owing to the reducing action of impurities or because of the easy reducibility of the solvent itself. The following alcohols were tested: n-propyl, isopropyl, n-butyl, isobutyl, tertiary butyl, isoamyl, tertiary amyl, n-hexyl, methylamyl, capryl, n-octyl, 2-ethylhexyl, nonyl, decyl, undecyl, dodecyl, cetyl, oleyl, stearyl, benzyl, tetrahydrofurfuryl, cyclohexyl, 2-nitro-1-butyl, diacetone alcohol, ethylene glycol, glycerol, several amino alcohols, and various Cellosolve and Carbitol solvents.

V. CHEMICAL PROPERTIES

A. REACTIONS WITH COMMON CATIONS

Both normal and alkali acid selenites can be prepared readily by neutralizing selenious acid with the calculated quantity of alkali hydroxide or carbonate. These colorless crystalline compounds are moderately soluble. The alkali

selenites can be heated to red heat and above without decomposition. Unlike the alkali sulfites, these compounds do not react with free sulfur, selenium, polysulfides, or polyselenides to form addition products corresponding to thiosulfates and selenosulfates.

The alkaline earth selenites are precipitated as finely divided, white powders of high refractive index when appropriate solutions are mixed at the neutral point. These compounds dissolve easily in strong acids. Like the alkali selenites they are stable to heat at high temperatures.

Elements forming tetravalent cations precipitate highly insoluble selenites from strongly acid solutions; among these are tin, titanium, cerium, zirconium, thorium, and lead. Ceric selenite is bright yellow in color, while the remaining selenites of this group are colorless. Other elements that form insoluble selenites in acid solutions are iron (Fe^{+++}), lead (Pb^{++}), mercury (Hg_2^{++}), and silver (Ag^+). Under certain conditions freshly precipitated metal hydroxides, such as ferric hydroxide and chromic hydroxide, quantitatively remove selenite from solution by forming insoluble adsorption compounds (181, 238). One method for the separation of selenite from copper solutions is based on this reaction with ferric hydroxide. Complex selenito-molybdates and -vanadates also can be precipitated from acid solutions containing certain heavy metal ions. The selenites of copper, nickel, zinc, and cadmium separate from weakly acid or neutral solutions. In general, the heavy metal selenites are much less stable to heat in comparison to the alkali and alkaline earth selenites. At comparatively low temperatures they decompose to yield the metal oxide and selenium dioxide or in certain cases metal oxide and selenide, free selenium, and oxygen.

B. INORGANIC OXIDIZING AND REDUCING AGENTS

While nitric acid oxidizes selenium to selenite, further oxidation to selenate appears to be impossible with this reagent or with nitric oxide at 315°C., according to Barnes (13). Stronger oxidizing agents such as fluorine, ozone, peroxide, chromate, dichromate, permanganate, chlorate, and perchlorate, however, can oxidize selenium or selenite to the hexavalent state. Selenite also is partly oxidized to selenate and in part reduced to selenium and hydrogen selenide by electrolysis. Chlorine and bromine oxidize selenium only to the tetravalent state, while iodine has little effect.

Selenium dioxide and selenites are easily reduced to free selenium by inorganic reducing agents, and many methods for the qualitative and quantitative analysis of selenium or selenite are based on such reactions. Iodide, sulfide, sulfite, bisulfite, thiosulfate, hypophosphite (120), stannous compounds, ferrous salts, hydrazine, and hydroxylamine are some of the reducing agents used for this purpose. Schott, Swift, and Yost (219) have shown the reaction of selenite with iodide to be reversible, and equilibrium measurements at 25°C. enabled them to calculate the free energies of un-ionized and ionized selenious acid.

Selenious acid is reduced to free selenium and in many cases to selenide by the action of nascent hydrogen. All metals, with the exception of gold and the platinum metals, reduce selenious acid apparently in this manner when immersed in the acid. In the presence of hydrochloric acid and selenious acid, silver

becomes covered with a film of silver selenide, this reaction being sensitive to one part of selenium in 50,000 parts of solution.

Gaseous substances such as hydrogen, ammonia, and phosphine reduce selenium dioxide with the emission of light and heat to form selenium and, under certain conditions, hydrogen selenide. Carbon reduces selenium dioxide to selenium, according to Berzelius. Carbon monoxide, however, does not appear to react even when activated by sunlight or ultraviolet light, and Barnes (14) found it possible to sublime selenium dioxide unchanged with carbon monoxide in a quartz tube. Sulfur, phosphorus, arsenic, boron, and silicon reduce the dioxide on heating. Dry sulfur dioxide is said to have no effect on selenium dioxide.

While selenic acid contains more oxygen than selenious acid, many of the reducing agents that react rapidly with selenite reduce selenate to selenium at a much slower rate. Selenic and selenious acids appear to be comparable to perchloric and chloric acids in this respect. On the other hand, in some instances selenic acid shows oxidizing properties comparable to the peroxides, since it is quantitatively reduced to selenious acid on boiling with hydrochloric or hydrobromic acids, chlorine and bromine being evolved in this reaction. Selenates also can be reduced to selenite by treatment with ferrous salts in acid solutions (250).

In an earlier review relating to the industrial uses of selenium and tellurium (252), it was pointed out that selenium dioxide and selenic acid are less stable than corresponding sulfur and tellurium compounds, as shown by the following heats of formation expressed in kilogram-calories:

	kg.-cal.		kg.-cal.
SO_2 (l)	75.27	H_2SO_4 (l)	189.75
SeO_2 (s)	57.08	H_2SeO_4 (l)	126.6
TeO_2 (s)	78.3	H_2TeO_4 (aq.)	169.5

The following similar figures are quoted from Yost and Russell (263):

	HEAT OF FORMATION	FREE ENERGY OF FORMATION	STANDARD ENTROPY S^0_{298}
	18° calories	calories	calories per degree
SO_2	70,920	−69,660	59.4 (gas)
SeO_2	56,360		62.5 (gas)
TeO_2	77,580	−64,320	17.4 (solid)

MOLAL FREE ENERGIES OF FORMATION F^0_{298}	
	calories per mole
SO_2 (g)	−71,735
SeO_2	
H_2SO_3	−128,535
H_2SeO_3	−101,361
SO_3^{--}	−116,400
SeO_3^{--}	−87,890

This marked difference in the heats and free energies of formation may explain why selenium dioxide, selenites, and selenates have outstanding oxidizing properties in comparison to their tellurium and sulfur analogues; that is, oxygenated selenium compounds are able to give up their oxygen more readily to reducing agents. Fisher and Eisner (77) find that tellurium dioxide, for example, is far less satisfactory than selenium dioxide as an oxidant for organic compounds.

A clearer expression of the oxidizing power of selenites and selenates is afforded by comparing the potential values relating to the important oxidation states of sulfur, selenium, and tellurium and their compounds in acid solution. The equations given below are taken from *Oxidation Potentials* by Latimer (132).

Zerovalent to tetravalent state (acid solution)

$$3H_2O + S = H_2SO_3 + 4H^+ + 4e^- \qquad E^0 = -0.45 \text{ v.}$$
$$3H_2O + Se = H_2SeO_3 + 4H^+ + 4e^- \qquad E^0 = -0.74 \text{ v.}$$
$$2H_2O + Te = TeO_2 \text{ (s)} + 4H^+ + 4e^- \qquad E^0 = -0.529 \text{ v.}$$
$$2H_2O + Te = TeOOH^+ + 3H^+ + 4e^- \qquad E^0 = -0.559 \text{ v.}$$
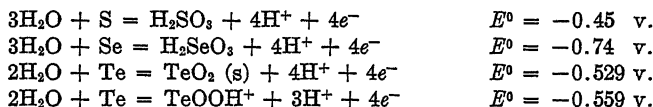
Tetravalent to hexavalent state (acid solution)

$$H_2O + H_2SO_3 = SO_4^{--} + 4H^+ + 2e^- \qquad E^0 = -0.20 \text{ v.}$$
$$H_2O + H_2SeO_3 = SeO_4^{--} + 4H^+ + 2e^- \qquad E^0 = -1.15 \text{ v.}$$
$$4H_2O + TeO_2 = H_6TeO_6 \text{ (s)} + 2H^+ + 2e^- \qquad E^0 = -1.02 \text{ v.}$$
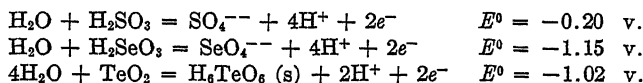
It may be of interest to note that Carter, Butler, and James (39) observed that selenium, although insoluble in hydrochloric acid, dissolves in concentrated hydrochloric acid in the presence of selenium dioxide. These authors measured the oxidation potential of the system selenium–selenium dioxide–concentrated hydrochloric acid and the effect of changes in concentration of selenium and selenium dioxide and found E (20°C.) to be -0.572 volt.

VI. Oxidation of Organic Compounds

A. MECHANISM OF THE REACTION

Selenium dioxide functions as a mild oxidizing agent over a wide temperature range, and oxidations of organic compounds with this substance have been likened to autoöxidation or peroxidation (64, 69). At ordinary temperatures, specific oxidation takes place as follows: in compounds containing methylene or methyl groups activated by an adjacent double bond, carbonyl, or aldehyde group, or adjacent benzene nucleus, the activated group is oxidized to the corresponding ketone or aldehyde group. Adjacent nitrogen atoms in heterocyclic compounds also activate the oxidation of the methylene or methyl group. Some of these oxidations can be carried out at room temperature with the aid of sunlight or ultraviolet light. Yields and the types of oxidation products obtained are affected by the solvent used. In glacial acetic acid, acetic anhydride, and sometimes in alcohol solvents the reaction generally proceeds only as far as the alcohol stage. Many instances have been described in which selenium dioxide acts chiefly as a mild dehydrogenating agent; however, it is rarely that this oxidant splits the C—C chain in the way that lead tetraacetate does.

Even at temperatures of 350–400°C. and above, where the specific oxidizing action of selenium dioxide is less pronounced, this oxidant exhibits unique characteristics. Emeleus and Riley (64) have observed that photographs of the flame spectra obtained by burning ammonia and diverse organic compounds in selenium dioxide vapor are identical in the visible region and show no lines in the ultraviolet spectrum. Inasmuch as selenium burning in oxygen alone gives an identical spectrum, and the water bands are not excited as is usually the case with burning hydrocarbons, their results prove definitely that the chief emission from the flames of compounds burning in selenium dioxide vapor is characteristic of selenium and perhaps of its oxide but not of the substance undergoing oxidation. These authors conclude that the selenium dioxide molecule possibly forms a definite intermediate compound with the substance undergoing oxidation (analogous to peroxidation) and the selenium is eliminated at a relatively low temperature, leaving intermediate oxidation products that undergo a non-luminous thermal decomposition, while radiation from the selenium molecule occurs readily and the decomposition of the intermediate yields enough energy to excite the selenium vibrations. In a study of the mechanism by which alcohols are oxidized with selenium dioxide, Melnikov and Rokitskaya (153) have shown that the lower alcohols react with the dioxide to form dialkyl selenite esters and that these intermediate products, when heated to 300°C. in a nitrogen stream, decompose to form the corresponding aldehyde, selenium, and water. Intermediate oxidation products containing selenium also have been isolated in many other reactions carried out at ordinary temperatures; therefore, this view of the mechanism of the oxidation appears to be well established.

In the type of oxidations discussed up to this point, selenium dioxide undergoes reduction to free selenium and the reaction stops when the dioxide has been completely utilized in this manner. Most of the precipitated selenium is recoverable and can be reoxidized to selenium dioxide for further use. In hot concentrated sulfuric acid, however, it is possible for selenium and selenium dioxide to function as catalytic agents.[3] The oxidizing action of selenium dioxide in sulfuric acid has long been known, and a test for the identification of alkaloids by their color reactions with this reagent has often been used in the past. Selenium, alone or in conjunction with mercury, has been found to act as a powerful catalyst in the Kjeldahl method for the analysis of nitrogen using concentrated sulfuric acid (29, 133, 165). The catalytic action of selenium in the concentrated sulfuric acid solution is thought to be caused by its ability to function as a reversible oxidizing and reducing agent in the manner shown by the following equations, according to Sreenivasan and Sadisivan (229):

[3] R. E. Schmidt (Bull. soc. ind. Mulhouse 84, 430 (1914); see J. Houben, *Das Anthracen und die Anthraquinone*, p. 323, Georg Thieme, Leipzig (1929)) discovered that the oxidation of anthraquinone and its derivatives by fuming sulfuric acid with the introduction of phenolic groups (Bohn–Schmidt reaction) is catalyzed by traces of selenium or mercury. It was thought that selenium acted as a catalyst, possibly in the following manner:

$$SeO_2 = Se + O_2$$
$$Se + 2SO_3 = SeO_2 + 2SO_2$$
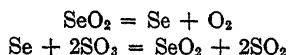
(1) $Se \leftrightarrows SeO_2 \leftrightarrows SeO_3$

(2) $Se \leftrightarrows SeO_2$ (mercury absent)

(3) $SeO_2 \leftrightarrows SeO_3$ (mercury present)

In the presence of mercury the reversible system (equation 1) predominates; in the absence of mercury, equation 2 represents the probable reaction. In either case selenium acts as a carrier for oxygen, and the oxygen is rendered active for the rapid oxidation of organic matter. As the result of a comprehensive study of reactions in concentrated sulfuric acid, Milbauer (166–168) and Milbauer and Mikolasek (169) similarly conclude that selenium functions as a catalyst in this medium. These authors show that selenium dissolves unchanged in concentrated sulfuric acid below 200°C. to give a grass-green solution. Oxidation of selenium to selenium dioxide proceeds slowly at approximately 200°C. and is complete at 300°C.

$$Se + 2H_2SO_4 \rightarrow SeO_2 + 2SO_2 + 2H_2O$$

Mercury appears to catalyze this oxidation of selenium by sulfuric acid and in addition undergoes further reaction as follows:

$$SeO_2 + 2HgSO_4 \rightarrow Hg_2SO_4 + SeO_3 + SO_3$$
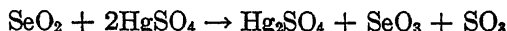
B. ORGANIC OXIDATIONS BY TYPES

1. Saturated compounds

Saturated hydrocarbons, alcohols, ethers, acids, esters, and most halogenated compounds are not attacked by selenium dioxide at low temperatures; however, oxidation may occur at higher temperatures.

In discussing the solubility of selenium dioxide in alcohols, it was indicated that the lower alcohols dissolve the dioxide at ordinary temperatures by forming alkyl acid selenites and that the selenium dioxide is recovered unchanged on evaporating the alcohol. Dialkyl selenite esters result at higher temperatures and the methyl, ethyl, propyl, butyl, and isobutyl esters have been prepared in this manner by Melnikov and Rokitskaya (153). These esters decompose to form the corresponding aldehyde, selenium, and water upon heating at 300°C. in a nitrogen atmosphere, while further oxidation of the aldehyde produces carbon dioxide in most cases. Emeleus and Riley (64) observe that ethyl ether and methyl, ethyl, and propyl alcohols burn completely with a characteristic moonlight-like flame in selenium dioxide vapor at about 400°C. and state that intermediate oxidation products are formed when the oxidation occurs at lower temperatures. Astin, Newman, and Riley (7) report that glyoxal is obtained in 5 per cent yield when ethanol is reacted at 230°C., while n-propyl and n-butyl alcohols give complex products, including some alkyl selenite.

On the other hand, certain alicyclic saturated alcohols are reactive at comparatively low temperatures. Menthol, for example, is oxidized and dehydrogenated on refluxing with selenium dioxide and ethanol to form hydroxythymoquinone, thymol, and menthane (106), while borneol and isoborneol give camphorquinone in 60 per cent yield (3, 106).

Lead tetraacetate oxidizes glycols and other polyhydroxy compounds at comparatively low temperatures by splitting the —CHOH—CHOH— linkage, but selenium dioxide does not appear to react except possibly to form addition products analogous to the alkyl acid selenites. Astin and Riley (8) were able, however, to oxidize methyl tartrate and ethyl tartrate with selenium dioxide and to obtain small amounts of methyl fumarate and ethyl ketohydroxysuccinate, respectively. This would seem to indicate that this reagent shows a mild dehydroxylating or oxidizing action with certain types of polyhydroxy compounds.

The following observations are of interest with respect to the oxidation of other types of saturated compounds: Glyoxal, acetic acid, and carbon dioxide are formed when ethane reacts with selenium dioxide vapor at 350–400°C. (198). While formic and acetic acids can be refluxed unchanged with selenium dioxide, propionic acid is oxidized to pyruvic acid in 2 per cent yield under comparable conditions (54). Acetic anhydride is satisfactory as a solvent for carrying out other oxidations, but under prolonged refluxing alone with selenium dioxide it yields 17 per cent of glyoxylic acid (187). Saturated fatty acids, such as lauric, myristic, palmitic, and stearic, are dehydrogenated to undecene, tridecylene, pentadecene, and heptadecene, respectively, on heating at 300°C. with selenium dioxide in sealed tubes, according to Yokoyama (261). Ethyl acetoacetate is oxidized at 90°C. in small yield to ethyl α,β-diketobutyrate (177); diethyl malonate yields 32 per cent of ethyl mesoxalate (7, 194, 196) and some diethyl dihydroxymalonate at 130°C. (177); diethyl succinate is dehydrogenated at 170°C. to ethyl hydrogen fumarate and fumaric acid (7); while ethyl malate yields ethyl diketosuccinate and degradation products under certain conditions (6).

2. Unsaturated compounds

Selenium dioxide readily oxidizes methylene or methyl groups adjacent to the double bond in many unsaturated aliphatic, alicyclic, and polycyclic compounds such as the terpene hydrocarbons. Ordinarily, a ketone or aldehyde results, but oxidation may be stopped at the alcohol stage by using glacial acetic acid or acetic anhydride as solvent. The oxidation product then is usually isolated as the acetate. In all cases the double bond is preserved when the reaction is carried out at ordinary temperatures. Compounds containing a triple bond are attacked adjacent to this bond, although a few cases are known in which selenium dioxide adds oxygen directly at the bond.

Methylene and methyl groups adjacent to a benzene nucleus also are activated and are oxidized to ketones and aldehydes or carboxylic acids. Benzene itself does not react with selenium dioxide except at high temperatures in the vapor phase; however, polycyclic aromatics such as naphthalene, anthracene, phenanthrene, etc., are attacked to varying extent at lower temperatures.

(a) *Unsaturated aliphatic compounds:* In the gaseous state at 220–240°C., ethylene reacts with selenium dioxide to produce glyoxal in yields of more than 80 per cent (138, 195, 197, 198), while methylglyoxal is formed in 19 per cent yield from propylene (198) indicating, therefore, that selenium dioxide shows a

tendency to saturate the double bond at high temperatures. Dreyfus also claims the use of selenium dioxide along with other catalysts for converting olefins to glycols and oxides (58).

At lower temperatures, in the presence of a solvent, all unsaturated aliphatic hydrocarbons appear to react at positions adjacent to the double bond. A comprehensive study of many types of these hydrocarbons has been made by Guillemonat (89).

Pulverized selenium dioxide is introduced slowly into a mixture of acetic acid, acetic anhydride, and excess hydrocarbon with continuous stirring to prevent the dioxide from settling to the bottom of the reaction flask. The mixture is refluxed for 10 hr., excess acetic acid and acetic anhydride are removed by washing with water, and the crude acetate is steam distilled. Saponification of the acetate with barium hydroxide yields the alcohol oxidation product. Various solvents can be used, including pyridine, ethanol, xylene, and water, but acetic acid appears to be most favorable both as to yield and as to quality of product. Hydrocarbons having completely substituted ethylenic carbon atoms are only partly oxidized and the oxidation occurs on the carbon atom in the alpha position to the substituted carbon: thus, for example, $RCH_2C(CH_3)=CCH_3$ is oxidized to $RCHOHC(CH_3)=CCH_3$. The rates of oxidation are so different that only one of the possible alcohols forms if the radicals in the alpha position are different; in order of decreasing ease of oxidation the radicals are CH_2, CH_3, and CH. Hydrocarbons having neither ethylenic carbon atom completely substituted also are oxidized in the alpha position to the ethylenic carbon. The CH_2 radical again is oxidized more readily than CH_3, and if present on each side of the ethylenic carbon atoms both CH_2 groups are oxidized to form a mixture of alcohols. A double bond at the end of a chain is as active as a bi-secondary bond but, owing to transposition, a primary alcohol forms instead of a secondary alcohol; for example, 1-hexene yields 2-hexen-1-ol.

To explain some of these reactions, Guillemonat suggests the following equations, in which R is a radical having an ethylenic bond:

(1) $4RCH_2H + SeO_2 \rightarrow (RCH_2)_4Se + 2H_2O$

(2) $(RCH_2)_4Se + H_2O \rightarrow (RCH_2)_2Se + RCH_3 + RCH_2OH$

(3) $(RCH_2)_2Se + H_2O \rightarrow RCH_2OH + RCH_3 + Se$

Equations 2 and 3 show that a portion of the original hydrocarbon is recovered unchanged even when the theoretical amount of selenium dioxide is used. The formation of an alkyl acetate also is explained, since acetic acid may supplant water in the same equations.

Selenium dioxide also appears to oxidize the carbon atom adjacent to the double bond in unsaturated compounds of greater complexity. Practical application of this fact has been suggested by Turk, Dawson, and Soloway (245), who propose a method for the synthesis of conjugated fatty oils by the oxidation of olive, linseed, cottonseed, castor, and other unsaturated oils with selenium dioxide in an alcoholic medium and subsequent dehydration of the hydroxylated product to form a conjugated material. Linseed oil treated in this

manner with only enough selenium dioxide to hydroxylate one fatty acid chain of the linseed oil molecule yields a final product showing a diene value of 24.8 and indicating 86 per cent conjugation of the one fatty acid chain. The same procedure with cottonseed oil gives a final product having a diene number of 17.9 and indicating about 62 per cent conjugation.

Backer and Strating (9) show that substituted butadiene derivatives, but not butadiene itself, react with selenious acid in chloroform solution at room temperature to form cyclic selenones:

$$RC=CH_2 \atop RC=CH_2 \quad + \ SeO_2 \ \rightarrow \quad {RC-CH_2 \atop RC-CH_2}\!\!\diagdown\!\!\diagup SeO_2$$
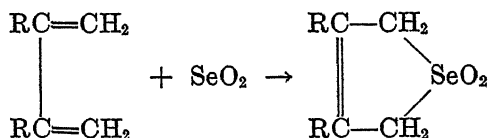
These products are not very stable and are decomposed readily by moisture on standing. However, in a study of polyene synthesis from certain hydrocarbons having two non-conjugated ethylenic bonds in the same molecule, J. Schmitt (218) has made the important observation that selenium dioxide acts as a selective dehydrogenating agent at fairly low temperatures and makes possible the preparation of compounds containing a conjugated series of double bonds. Tetraphenylhexatriene is obtained from 1,1,6,6-tetraphenyl-1,5-hexadiene by refluxing with acetic acid and selenium dioxide, while 1,6-dibiphenylene-hexatriene is prepared in the same way from 1,6-dibiphenylene-1,5-hexadiene.

The few acetylenic hydrocarbons that have been studied appear to react with selenium dioxide in about the same manner as corresponding ethylenic hydrocarbons. Truchet (242) prepared 3-hydroxy-1-heptyne in 27 per cent yield by reacting 1-heptyne and selenium dioxide in ethanol, while 3-hydroxy-1-octyne was obtained from 1-octyne. On the other hand, Truchet (243) showed that methylphenylacetylene appeared to add selenium dioxide and give a product that was hydrated in alkaline solution to ethyl phenyl ketone.

(b) *Unsaturated alicyclic compounds:* Guillemonat (89) observed that in unsaturated alicyclic hydrocarbons with substituted ethylenic carbon atoms, oxidation in acetic acid plus acetic anhydride solution occurs in the alpha position to the most substituted carbon atom and also in the cycle if it is possible. Oxidation of the CH group leads to conjugated dienes as the result of dehydration of the tertiary alcohol formed, and conjugated dienes may also result from the oxidation of hydrocarbons having cyclic bi-tertiary double bonds. For example, 1-ethylcyclohexene yields the acetate of 1-ethylcyclohexen-6-ol; 1,6-dimethyl-cyclohexene is oxidized to five fractions, each fraction containing o-xylene and 2,3-dimethyl-1,3-cyclohexadiene with an undetermined liquid; while 1,2-dimethylcyclohexene yields one fraction consisting of o-xylene and 2,3-dimethyl-1,3-cyclohexadiene and a second fraction containing a mixture of one ethylenic acetate and one dienic acetate.

While not so reactive as compounds having double-linked tertiary carbon atoms, alicyclic hydrocarbons with bi-secondary ethylenic bonds give yields as high as 30–40 per cent. The alpha position is attacked and the CH_2 group is

more reactive than CH, with both alpha CH$_2$ groups being oxidized simultaneously. Transpositions of the allylpropenylic type occur readily in certain cases. Thus, cyclohexene yields the acetate of 1-cyclohexen-3-ol; 3-methylcyclohexene gives 6-methylcyclohexanol and small amounts of toluene, 4-methylcyclohexene, and 4-methylcyclohexen-3-ol; and 4-methylcyclohexene forms a mixture of the acetates of 4-, 5-, and 6-methylcyclohexen-3-ols, with the first predominating. In conjunction with the three equations proposed by Guillemonat to explain the mechanism by which unsaturated aliphatic compounds are oxidized, the following equation is proposed by him to explain the formation of dienes having conjugated systems:

$$(CH_3CH{=}C(CH_3)CH_2)_2Se \rightarrow CH_2{=}CHC(CH_3){=}CH_2 + (CH_3)_2C{=}CHCH_3 + Se$$

In the presence of selenium dioxide cyclohexene is oxidized by hydrogen peroxide to *trans*-cyclohexanediol in 45 per cent yield; 1,2-diols also result on oxidizing cyclopentadiene and piperylene under the same conditions (225).

Monocyclic terpene hydrocarbons are oxidized by selenium dioxide in much the same manner as the simpler unsaturated alicyclic compounds with the carbon atom adjacent to the double bond being attacked. Δ^1-Menthene gives carvotanacetone, while Δ^3-menthene yields Δ^3-menthen-5-one, according to Borgwardt and Schwenk (25, 223, 224). α-Phellandrene, with two double bonds in the ring, reacts to give cuminaldehyde and *p*-cymene, both materials being dehydrogenation products (25, 104).

(c) *Unsaturated polycarbocyclic compounds:* Bicyclic terpene hydrocarbons react quite readily with selenium dioxide at moderate temperatures. Usually, a complex mixture of products results and the yields depend on temperature, time of reaction, solvent, and the amount of selenium dioxide used. A review of the existing literature dealing with the oxidation of β-pinene is instructive from this standpoint. Dupont, Allard, and Dulou (59) obtained what they thought was pure pinocarvone in 35 per cent yield by refluxing a mixture of β-pinene, selenium dioxide, and alcohol, while Zacharewicz (265) showed that both pinocarvone and pinocarveol were formed. In a careful study of this reaction, Stallcup and Hawkins (230) treated β-pinene in molar ratio with selenium dioxide alone, and in water, alcohol, acetone, benzene, hexane, ether, carbon tetrachloride, and pyridine for approximately an average time of 10 hr. to obtain 15–34 per cent of a steam-volatile product that was shown to contain mostly carvopinone with some pinocarvone. Joshel and Palkin (117), however, demonstrated that pinocarveol was obtained as the main product in 42 per cent yield by the reaction of β-pinene in ethanol with slightly less than 0.5 mole of selenium dioxide per mole of β-pinene. Finally, Stallcup and Hawkins (231) showed that in acetic acid or acetic anhydride the products were largely pinocarvyl acetate with some pinocarveol, carvopinone, and pinocarvone. All of these investigators observed the fact that much of the selenium remained in the non-volatile reaction products in the form of complex, organic selenium compounds. In the case of the reaction of camphene with selenium dioxide, Zacharewicz (264) obtained camphene selenide as the sole product.

The effect of temperature on the type of product obtained is well illustrated by the work of Campbell and Harris (37), who oxidized $\Delta^{9,10}$-octalin with selenium dioxide in acetic anhydride: $\Delta^{9,10}$-octalol-1 acetate was obtained at 5°C., $\Delta^{9,10}$-octalindiol-1,5 diacetate at 30°C., and a hexahydronaphthalenediol-1,5 diacetate was isolated as the main product upon carrying out the reaction at 120°C.

(d) *Aromatic compounds:* Selenium dioxide attacks methyl or methylene groups attached to a benzene nucleus, but these reactions generally require high temperatures and give low yields of oxidation products. Many aromatic derivatives, however, are attacked vigorously at low temperatures to form resinous products of unknown constitution. Among these are phenols, cresols, aminophenols, phenol ethers, and amines. Amine reactions are discussed more fully in the section on nitrogen compounds, and it is shown further on that definite organic selenium compounds can be isolated by reacting phenolic compounds with selenium dioxide in concentrated sulfuric acid.

Toluene is oxidized by selenium dioxide to benzoic acid in only 27 per cent yield at 300°C. in a sealed tube (54). Dinitro- and trinitro-toluenes are unaffected on refluxing with selenium dioxide in alcohol (76). At 300°C. dibenzyl reacts to produce both stilbene and benzil; in this reaction stilbene is formed first by dehydrogenation and then is oxidized to benzil, according to Deupree and Lyons (54). Stilbene itself yields 86 per cent benzil at 260–280°C. (6) and tolane gives a 35 per cent yield of benzil at 280°C. (187). Diphenylmethane appears to undergo oxidation more readily than triphenylmethane (76). Compounds containing partly substituted methyl groups adjacent to the benzene nucleus are more reactive. For example, at reflux temperatures benzyl alcohol is converted completely to benzaldehyde, while benzyl chloride and p-nitrobenzyl chloride lose chlorine and give the corresponding aromatic aldehydes in about 50 per cent yield (76).

Polycyclic aromatic hydrocarbons differ greatly in their ease of reaction with selenium dioxide. Anthraquinone is obtained in about 75 per cent yield by treating anthracene in nitrobenzene (6) or molten anthracene and selenium dioxide without solvent (187). Phenanthrene (6, 187) and fluorene (187), however, produce only about 5 per cent yields of phenanthraquinone and fluorenone, respectively. On the other hand, Badger (10) states that 1,2,5,6-dibenzfluorene gives a satisfactory yield of 1,2,5,6-dibenzfluorenone. Acenaphthene and selenium dioxide in acetic acid at 150–200°C. yield a mixture of acenaphthylene glycol, acenaphthylene, polyacenaphthylene, and dinaphthylenecyclobutane; oxidation by lead tetraacetate yields only the last three products (173).

Although methyl groups attached to a polycyclic nucleus require a fairly high temperature for reaction, selenium dioxide has a definite use in this type of oxidation, since strong oxidizing agents such as chromic acid or permanganate often produce resinous products entirely. With selenious acid in an autoclave at 230–240°C., Kacer (121–123) claims that 2-methyl- and 6-methyl-benzan-

threnes are oxidized to the corresponding benzanthrenealdehydes, 5-methylnaphthanthraquinone forms a carboxylic acid, and 2-benzylbenzanthrone produces 2-benzoylbenzanthrone. Copp and Simonsen (50) report that 9- and 10-methylmesobenzanthrones are oxidized to the corresponding mesobenzanthronealdehydes in approximately 25 per cent yield. Similarly, with selenium dioxide in nitrobenzene, 2-methyl-1,1'-dinaphthyl ketone produces 2-carboxy-1,1'-dinaphthyl ketone, whereas permanganate oxidation does not give any useful products (49).

(e) *Complex unsaturated compounds:* Much work has been done in the recent past on the structure and synthesis of naturally occurring sterols, bile acids, sex hormones, sapogenins, polyterpenes, and other complex compounds. As would be expected, selenium dioxide, among other reagents, has been used in these studies as an aid in elucidating the structure of certain products and for the preparation of new derivatives. Specific compounds oxidized and the products obtained are listed in table 3 at the end of this review.

In their work on sterols and bile acids Callow and Rosenheim (35) showed that selenium dioxide acted mainly as a dehydrogenating agent upon reacting with ergosterol, α-ergostenol, and apocholic acid, whereas oxide formation was the characteristic reaction with cholesterol and dihydroergosterol. Cholestenediols were obtained, however, by reacting cholesterol with selenium dioxide in alcohol, acetic acid, or nitrobenzene, as shown by Butenandt and Hausmann (33) and by Rosenheim and Starling (202). Montignie (175) proposed the use of selenious acid to differentiate ergosterol from other sterols, since ergosterol reacted with this reagent in 2 min. at 95°C., while cholesterol, phytosterol, and stigmasterol gave negative tests. Other references to work in this field are as follows: oxidation of cholesterol to cholestanone at 230°C. using elemental selenium (56); the treatment of cholesterol derivatives (63), lanosterol derivatives (19), clionastrol (21), sitosterol and stigmasterol derivatives (145, 146); the reaction of apocholic and norcholanic acid derivatives (34, 210); and the synthesis of substances related to the sterols (148).

The use of selenium dioxide for the preparation of sex hormone derivatives related to pregnenolone and androsterone has been reported by Marker, Crooks, and Wittbecker (144), Ruzicka and Plattner (209), and in several patents (164, 227, 228). Howeg and Herloff (108) claim in a patent that both selenium dioxide and lead tetraacetate break the cyclopentane ring in estradiol; if so, this is the first case to be reported of ring rupture by the use of selenium dioxide at ordinary temperatures.

Studies relating to the oxidation of complex polyterpene compounds with selenium dioxide have been made by Bilham, Kon, and Ross (22), Jones and Meakins (116), Mowrer, Green, and Spring (176), Picard and Spring (185), and Ruzicka and his collaborators (204–208, 211). Sapogenin derivatives have been studied by Marker (143) and by Marker and Turner (147). Osajetin and pomiferitin compounds derived from osage orange pigments have been reacted with selenium dioxide by Wolfram and Mahan (258).

3. Oxidation of aldehydes and ketones

The discovery made by Riley (194) that selenium dioxide exerts a specific oxidizing action on methyl and methylene radicals adjacent to the carbonyl group in aldehydes and ketones has been widely applied to the preparation of many previously inaccessible glyoxal, α,β-diketone, and triketone derivatives from aliphatic, alicyclic, aromatic, and terpene aldehydes and ketones. The rather good yields obtained in these reactions are remarkable because of the ease with which the oxidation products polymerize under normal conditions.

Riley, Morley, and Friend (200) obtained methylglyoxal in 60 per cent yield from acetone and almost a 100 per cent yield of glyoxal from acetaldehyde. They found in general that the higher ketones and aldehydes were less reactive than the first members of each series. Methyl groups appeared to be more reactive than methylene, as shown by the fact that ethyl methyl ketone produced mainly ethylglyoxal rather than biacetyl. Likewise, a comparison of the reactivity of acetophenone and phenylacetaldehyde led to the same conclusion, since these compounds gave phenylglyoxal in yields of 50 and 35 per cent.

The mechanism by which aldehydes and ketones are oxidized with selenium dioxide has been studied in detail by Melnikov and Rokitskaya (154, 156–160). These authors state (154) that carbonyl compounds are oxidized chiefly to aldehydo ketones and α,β-diketones with organic selenium compounds, products of deeper oxidation being formed in smaller amounts. Acetone and butyraldehyde react rapidly, whereas triacetonemannitol and the acetal of butyraldehyde oxidize only after some hydrolysis has occurred, thus making it apparent that carbonyl compounds react only through their enol forms. Selenious acid adds to produce enol esters (analogous to the reaction of alcohols with selenium dioxide), and these decompose in the manner suggested by Melnikov and Rokitskaya (153) and previously discussed in the section dealing with the oxidation of saturated compounds. The reactions of acetone, ethyl methyl ketone, methyl n-propyl ketone, and cyclohexanone with selenium dioxide are bimolecular. Since selenious acid reacts with amylene and cyclohexene by adding to the double bond, with the addition compound decomposing to give organic selenium compounds, aldehydes, alcohols, and hydrocarbons of higher molecular weight, it is inferred that products of deeper oxidation of carbonyl compounds probably result from similar addition of selenious acid to the double bond of the enol form.

The kinetics of ketone oxidation by selenium dioxide were studied (156), with additional experimental evidence given to show that these oxidations are bimolecular reactions. Equivalent amounts of ketone and selenious acid in 75 per cent acetic acid were reacted at 20° and 50°C. for 1 to 6 hr. The selenium precipitated during the course of each reaction was collected, washed with water and ether, and dried to constant weight at 100°C. The comparative graphs, obtained by plotting selenium recovered versus time, for a series of symmetrical alkyl ketones and for a series including unsymmetrical alkyl ketones, acetophenone, and pinacolone, indicate that the rate of oxidation (enolization) decreases gradually with increasing molecular weight. This is shown also by

alkyl aryl ketones in the series from methyl phenyl ketone to ethyl phenyl ketone and phenyl *n*-propyl ketone. Alicyclic ketones are more rapidly oxidized than aliphatic ketones, which in turn are more easily oxidized than aromatic ketones. The gradual decrease in the oxidation rate of methyl propyl ketone, isopropyl methyl ketone, and pinacolone shows the influence of primary, secondary, and tertiary radicals on the degree of enolization. Oxidation of isomeric amyl methyl and hexyl methyl ketones (160) shows that the oxidation velocity depends greatly on structure. Ketones containing an even number of CH_2 groups between the carbonyl group and a secondary radical are less easily enolized than normal ketones or those ketones containing an odd number of CH_2 groups between the carbonyl group and a secondary radical. Ketones having a secondary or tertiary group attached to carbonyl are still less easily enolized. At 30°C. in 75 per cent acetic acid the order of increasing oxidation rate for a series of substituted acetophenones (159) is m-$NO_2C_6H_4COCH_3$, p-$BrC_6H_4COCH_3$, p-$ClC_6H_4COCH_3$, $C_6H_5COCH_3$, p-$CH_3OC_6H_4COCH_3$, p-$CH_3C_6H_4COCH_3$, p-$IC_6H_4COCH_3$, and $C_6H_5CH_2COCH_3$.

A study of the oxidation of acetone, ethyl methyl ketone, and methyl propyl ketone in absolute and aqueous methanol, ethanol, butanol, isobutyl alcohol, and isoamyl alcohol indicates that the relation of rate constants to the structure of the ketones is the same as for their reaction in 75 per cent acetic acid (158). The constants are lower in the anhydrous alcohols than in the acetic acid, owing to the formation of complexes between the alcohols and the ketones. The addition of water decomposes these complexes and thereby increases the rate of oxidation. The reaction rate increases with the molecular weight of the normal alcohols and is highest in isobutyl alcohol solution.·

Oxidation, with selenious acid in 95 per cent acetic acid, of a series of aliphatic aldehydes (157) having normal and branched chains shows that the oxidation velocity decreases with increasing molecular weight with the exception of acetaldehyde, whose reaction constant is considerably smaller than that of propionaldehyde (explainable by the easy polymerization of acetaldehyde in acid medium). The reaction constant also is decreased in the iso compounds as compared with aldehydes having a normal chain.

The most interesting case of dehydrogenation of a ketone with selenium dioxide appears to be that reported by Armstrong and Robinson (4), who obtained diacetylethylene in 15 per cent yield from acetylacetone. This reaction appears to be comparable to the dehydrogenation of several 1,5-hexadiene derivatives to hexatrienes, as shown by Schmitt (218). Godchot and Cauquil (85) report that dehydrogenation products as well as the expected 1,2-diones are formed in the reaction of 1-methyl-2-, 1-methyl-3-, and 1-methyl-4-cyclohexanones with selenium dioxide in ethanol at 80°C. Under the same conditions cycloheptanone gives the 1,2-diene but cyclooctanone yields only 8-ethoxy-1,2-cyclooctandione. Hirayama (103, 104) finds that monocyclic terpene ketones such as menthone and piperitone are dehydrogenated in the ring to produce thymoquinone derivatives.

Camphor reacts with selenium dioxide in a normal manner, giving camphor-

quinone in 65 per cent yield (3). When the reaction is carried out in ethanol, toluene or xylene, or acetic anhydride the corresponding yields are 27, 88, and 95 per cent, according to Vene (248). Vene finds, however, that camphor derivatives exhibit rather unusual reactions, since α-bromo- and α-chlorocamphors lose halogen to form camphorquinone, while ethylcamphor yields both ethylidenecamphor and camphorquinone on heating with selenium dioxide alone. Benzylcamphor forms benzylidenecamphor in 95 per cent yield; benzylidenecamphor is remarkable in that it is unaffected by heating with selenium dioxide at 200°C. Furthermore, isonitrosocamphor is attacked by selenium dioxide in a unique fashion with scission of the ring to give fair yields of camphornitrile and camphoric anhydride.

The oxidation of a methylene group situated between two carbonyl groups to form a triketone has been accomplished in several cases. The oxidation of 1,3-diketohydrindene by selenium dioxide in dioxane solution furnishes the best method for the preparation of ninhydrin (triketohydrindene hydrate) (240a). Triketopentane is obtained in 12–25 per cent yield from acetylacetone by reaction with selenium dioxide alone or in ethanol (36, 186), and dimesityl triketone in good yield from di(β-isoduryloyl)methane (81). Nevertheless, Piutti (186) was unable to prepare a triketone from acetylbenzoylmethane, $CH_3COCH_2COC_6H_5$.

4. Oxidation of nitrogen compounds

Selenious acid, like other acids, combines with aliphatic and aromatic amines at low temperatures to form crystalline, substituted ammonium salts (6, 40, 54, 101). The direct addition of anhydrous selenium dioxide to an amine also may occur as shown in the case of piperidine, which reacts in cold benzene to produce the addition product $C_5H_{10}NH \cdot SeO_2$ (141, 142). With increasing temperature, both aliphatic and aromatic amines oxidize rapidly to yield complex resinous or tarry products. Aniline, for example, first forms aniline selenite and then more complex, dark blue to black compounds that are insoluble in water. The reaction between most amines and selenium dioxide is highly exothermic at high temperatures and usually proceeds with explosive violence. In concentrated sulfuric acid solution selenium dioxide gives characteristic color reactions and organic selenium compounds with aromatic amines and alkaloids. Aromatic o-diamines undergo a special reaction with selenium dioxide to form piaselenols. These compounds and the color reactions in sulfuric acid are discussed in following sections of this paper.

Heterocyclic amines having a tertiary nitrogen in the ring, such as pyridine and quinoline, may be refluxed with selenium dioxide without change. At 300°C. in a sealed tube acridine is hydrogenated in part to dihydroacridine (261).

Useful carboxyaldehyde and carboxylic acid derivatives of heterocyclic nitrogen compounds are obtained by reacting alkylated heterocyclic nitrogen compounds with selenium dioxide at moderate to high temperatures. Oxidations of this type are not much different from those shown by alkyl benzene derivatives, with the exception that the tertiary nitrogen appears to exert an activating

influence on an adjacent alkyl group. These oxidations are discussed from the viewpoint of the nitrogen system of compounds by Bergstrom (21a), who shows that the —N≡CH— group in nitrogen ring compounds is comparable in many of its reactions to the aldehyde group in the oxygen system. The activating influence of this aldehydic nitrogen group is transmitted to some extent along the carbon chain. For example, Henze (95) was able to obtain small yields of the corresponding pyridinealdehydes and pyridinecarboxylic acids from the reaction of 2- and 3-methylpyridines with selenium dioxide. Kwartler and Lindwall (130) describe the preparation of quinoline-4-aldehyde derivatives in 50–60 per cent yield from 4-methylquinoline and 6-methoxylepidine, using selenium dioxide in xylene as solvent.

The alkyl group adjacent to the tertiary nitrogen apparently is considerably more active than an alkyl group in the β-position. According to a patent by Henze and Henze (96), it is possible to separate a mixture of α- and β-alkylated pyridines by means of selenium dioxide, since the α-derivative is attacked preferentially. In heterocyclic nitrogen compounds having several alkyl groups, the α-alkyl group also is attacked first. Burger and Modlin (31) oxidized 2,3,8-trimethylquinoline to 3,8-dimethylquinoline-2-aldehyde and 2,3,8-trimethyl-5-nitroquinoline to 3,8-dimethyl-5-nitroquinoline-2-aldehyde. Henze (95) reports that 2-ethyl-3-methylquinoline forms 3-methylquinoline-2-carboxylic acid, the ethyl group being destroyed.

In repeating some of the work on the preparation of quinolinealdehydes from the corresponding homologs by direct oxidation with selenium dioxide, Kaplan (125) found that the best yields are obtained when the selenium dioxide is prepared shortly before use. If the selenium is stored unsublimed for upward of several months, it converts quinaldine into a benzoin-type compound (quinaldoin) instead of the aldehyde, and lepidine into 1,2-di-4-quinolylethylene. This anomalous behavior does not appear to result because of the presence of selenates, nor is it a catalytic effect.

Other interesting types of nitrogen compounds reported to have been oxidized by selenium dioxide are listed in the following references: isoquinoline derivatives to isoquinaldehydes by Burrows and Lindwall (32); methylnaphthoxazole and methylbenzimidazole to naphthoxazole- and benzimidazole-2-carboxaldehydes in a patent to the I. G. Farbenindustrie A.-G. (110); and the oxidation of hydroquinine to hydroquininone by McKee and Henze (140).

While it has been known for some time that phenylhydrazine reduces selenium dioxide (101) and can be used for the analysis of selenite (90, 174), it is only recently that this reaction has been studied in detail to determine the products formed. Postowskii, Lugovkin, and Mandryk (188) have found that several types of compounds are obtained from arylhydrazines, depending on the reaction conditions. In acid solutions arylhydrazines react first to form a diazonium salt, and the course of the reaction can be followed by coupling the diazonium salt with β-naphthol to form the azo dye. (Using α-naphthylamine in place of β-naphthol, Feigl and Demant (70) have shown this reaction to be a sensitive spot test for determining arylhydrazines, hydrazones, and osazones.) On

continued refluxing with selenious dioxide in acid solution, phenylhydrazine produces some tetraphenyltetrazine and a blue dye. In like manner, p-nitrophenylhydrazine gives good yields of p-nitrophenyltriazine and the compound p-$O_2NC_6H_4N$=$NNHC_6H_4NO_2$-p. By the use of selenium dioxide in alcohol the reaction is modified still more, with diphenylamine being obtained in 94 per cent yield from phenylhydrazine.

5. Oxidation of sulfur compounds

Alkyl and aryl thiols (mercaptans), thiol acids, thioamides, dithiocarbamates, dithiophosphates, thiourea, and thiourea derivatives in which enolization to form the —SH group is possible, all undergo ready oxidation with selenium dioxide or selenite ion to form disulfides along with selenium compounds in some cases. This type of reaction finds use in the preparation of rubber accelerators and for the analysis of selenium. Organic sulfides are oxidized to sulfoxides and sulfones (152).

Painter (183) prepared an unstable compound of the type RSSeSR by reacting cysteine at low temperatures with selenium dioxide in a solvent. Similar compounds were made by Bersin (21b) from thioglycolic acid and glutathione. Painter believes that the reaction between a thiol and selenium dioxide is best interpreted as follows:

$$2RSH + SeO_2 \rightarrow RS-Se-SR + H_2O$$
$$\downarrow$$
$$O$$

$$4RSH + SeO_2 \rightarrow RSSeSR + RSSR + 2H_2O$$
$$\downarrow$$
$$4RSH + SeO_2 \rightarrow 2RSSR + Se + 2H_2O$$
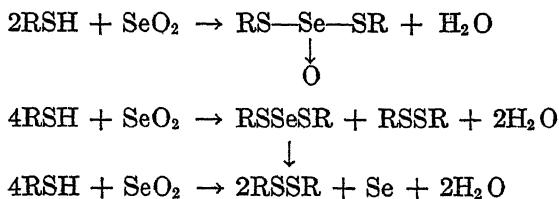
By reacting cysteine hydrochloride with sodium selenite Stekol (234) obtained selenium tetracysteine, $Se(SCH_2CHNH_2COOH)_4$. Tetravalent selenium compounds having useful vulcanization properties have been prepared by Russell (203) by treating secondary amines and carbon disulfide with selenium dioxide in an alcohol solvent. The dithiocarbamate formed from the secondary amine and carbon disulfide produces $(R_2NCS_2)_4Se$ in this reaction.

According to Werner (254) thiourea is oxidized to bis(aminoiminomethyl) disulfide by selenium dioxide, as shown by the following equation in which thiourea is written in the tautomeric form:

$$
\begin{array}{c}
NH \\
\parallel \\
4NH_2-C-SH
\end{array} + H_2SeO_3 \rightarrow 2\left[
\begin{array}{c}
NH \\
\parallel \\
NH_2 C-S-
\end{array}
\right]_2 + Se + 3H_2O
$$
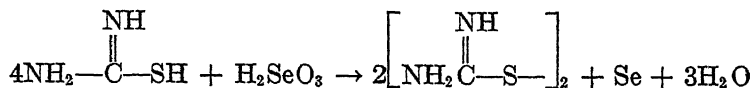
This reaction can be used for the quantitative analysis of selenious acid or thiourea or as a qualitative test for these substances, as shown by Falciola (66). Substituted thiourea derivatives, thioacetamide, and thiobenzamide appear to react in the same manner; consequently, Werner (255) proposed this as a qualitative test for the —SH group in organic compounds. Tetrasubstituted thiourea

compounds, as would be expected, do not react with selenium dioxide. A large number of substituted thiourea compounds were qualitatively examined for reaction with several metal ions and with selenite ion in an acid medium by Yoe and Overholser (260), who conclude that thiourea itself gives the most sensitive reaction.

Ivanov (114) first proposed the use of thiocyanate for the analysis of selenite and was able to isolate the unstable compound $(HSCN)_2 \cdot H_2SeO_3$ by adding selenious acid to an ammonium thiocyanate solution. This compound quickly changes over to free selenium. According to Ljung (136) and Hall (93) the reaction appears to be sensitive to one part of selenite in 20–38 million parts of solution if carried out in boiling hydrochloric acid solution. Ljung formulates the reaction as:

$$6H^+ + 2CNS^- + SeO_2 \rightarrow Se\ (s) + 2CN^- + 2S^- + H_2O$$

However, Hall believes that the principal products of the reaction are NH_4^+, CO_2, SO_4^{--}, and sulfur.

The use of a mixture of selenium dioxide and calcium chloride for differentiating various types of war gases has been suggested by Bradley (28). Liquid vesicants are brought in contact with the powder. In contact with droplets or a spray of Lewisite (β-chlorovinyldichloroarsine), the mixture becomes red instantly, owing to the reduction of selenium dioxide. Liquid "mustard gas" develops no red color until the powder is moistened with water, and in this case the maximum color intensity is not reached for about 5 min. Thiodiglycol reacts in the same manner.

6. Oxidation with selenium dioxide in concentrated sulfuric acid

The catalytic behavior of selenium and selenium dioxide in the medium of concentrated sulfuric acid has been discussed previously in the section of this paper relating to the mechanism of organic oxidations. It was also mentioned that practical use is being made of this property by employing selenium and selenium dioxide in sulfuric acid as catalysts for the rapid combustion of organic matter in the Kjeldahl method of analysis (29, 133, 165, 216). Another interesting application of this fact has been described recently by Woodward, Badgett, and Kaufman (259). These authors observe that selenium, selenium dioxide, and copper selenite function as effective catalysts in concentrated sulfuric acid for the liquid-phase oxidation of nicotine, β-picoline, and quinoline to nicotinic acid. At 250–330°C., and with a quantity of selenium catalyst equal to about 10 per cent by weight of the compound oxidized, the maximum yield of nicotinic acid obtained from either nicotine or quinoline is approximately 75 per cent of theoretical, and from β-picoline about 50 per cent of theoretical.

Long before the catalytic properties of selenium dioxide in sulfuric acid were recognized, a test was developed and widely used for the identification of alkaloids by their color reactions with this reagent. Studies of this reaction were made by Brandt (30), Dragendorff (57), Ferreira da Silva (73), Jouve (118), Lafon (131), Mecke (151), Orloff (181a), Schmidt (217), and Sergeeff (225a).

Conversely, spot tests were developed for the detection of selenite in sulfuric acid, using codeine phosphate (109, 192) and aspidospermine (184). Other compounds used for the same purpose were pyrrole (20, 213), diphenylamine (137), and acetylene (118).

More recent studies of Dewey and Gelman (55) dealing with the color reactions of nitrogen compounds have brought out the fact that color development with selenium dioxide in sulfuric acid is not a specific test for the alkaloids. This statement is supported by Levine (134), who similarly investigated the color reactions of phenols and phenolic ethers. Levine found that phenols brought in contact with concentrated sulfuric acid containing 0.5 per cent of selenium dioxide or 0.75 per cent of sodium selenite give rise to a color ranging from pale green to blue-green or purplish blue or the appearance of several colors simultaneously. On standing, or heating, or on the addition of water the characteristic color disappears and is replaced by a brown to brick-red color. The reaction appears to be very sensitive and widely applicable. The following types of phenols respond to the test: mono-, di-, and tri-phenols; phenolic ethers, aldehydes, alcohols, and acids; glycosides yielding phenols on hydrolysis; alkaloids having phenolic groups. Nitrated phenols give negative results. Levine explains the course of the reaction by saying that the phenolic body decomposes selenium dioxide to selenium and the latter dissolves in sulfuric acid with a green color owing to the formation of $SeSO_3$. This explanation probably is not tenable, since definite selenium compounds have been isolated (see table 1 of the following section) from reactions with selenium dioxide in sulfuric acid, as shown by Battegay and Hugel (15–17), Farbwerke vorm. M. L. G. B. (67, 68), and Zimmer & Cie (249). In any case, Levine concludes that color production appears to be a specific test for the phenolic hydroxyl group and that a positive reaction, therefore, cannot be accepted as indicative of the presence of the opium alkaloids unless other phenolic compounds are absent. This conclusion is modified further by Dewey and Gelman, who show that color production with the selenium dioxide reagent is not a specific reaction of phenolic compounds and that many nitrogenous compounds, especially those containing two or three aromatic nuclei, give intense color reactions with this reagent. The test provides a sensitive method for detecting and distinguishing between certain nitrogen compounds: for example, the colors produced by 1-naphthylamine, 2-naphthylamine, and di-2-naphthylamine can be readily distinguished; diphenylguanidine shows no color, but triphenylguanidine yields a pale blue changing to yellow. Dewey and Gelman declare that the test with selenium dioxide–sulfuric acid reagent for the presence of opium alkaloids cannot be considered conclusive unless interfering phenols and nitrogen compounds are known to be absent.

7. Reactions yielding organoselenium compounds

At several points in this discussion, attention has been directed to the fact that in many organic oxidations selenium dioxide appears to form addition compounds that decompose into oxidation products, complex organic selenium compounds, water, and selenium. Ordinarily only a small part of the selenium

can be recovered in the organically bound form, but Zacharewicz (264) reports one case in which camphene selenide is the sole reaction product from camphene and selenium dioxide. The literature on selenium dioxide discloses other types of reactions that lead to the formation of organoselenium compounds. These are listed in table 1.

Organoselenium compounds have been prepared from selenium dioxide in the Grignard reaction (126), in the Friedel–Crafts synthesis (40, 51, 97, 139), and by the reaction of selenium dioxide with other organometallic compounds (155). Direct addition occurs with substituted butadiene hydrocarbons (9), certain quaternary ammonium compounds (38), oxalic acid (83), a benzidine–acetone mixture (72), alcohols (6, 52, 101, 190), aniline (6, 54), and piperidine (141, 142). The reactions of organic compounds with selenium dioxide in concentrated sulfuric acid to form selenopyronines (15–17), aromatic selenium compounds (67, 68), and alkaloid-selenium compounds (249) are interesting because of the light they throw on the mechanism of color reactions obtained with phenols, aromatic nitrogen compounds, and alkaloids in this reagent.

Aromatic o-diamines and related compounds react with selenious acid or selenium dioxide to form an interesting series of compounds known as the piaselenols (18, 75, 94, 99–101, 215). The reaction takes place in water or alcohol solution at ordinary temperatures with the formation of a stable five-membered heterocyclic ring as follows, according to Hinsberg (99):

$$C_6H_4 \underset{NH_2}{\overset{NH_2}{\diagup\diagdown}} + SeO_2 \rightarrow C_6H_4 \underset{N}{\overset{N}{\diagup\diagdown}} Se + 2H_2O$$
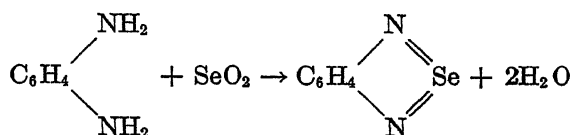
Peri-naphthylenediamine reacts in a different manner to produce di-peri-naphthoselendiazole (102, 214)

$$C_{10}H_6 \underset{NH}{\overset{N}{\diagup\diagdown}} Se \underset{N}{\overset{NH}{\diagup\diagdown}} C_{10}H_6$$
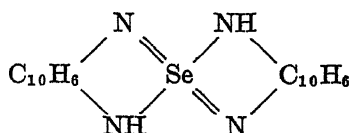
and dihydrodi-peri-naphthoselendiazole (102):

$$C_{10}H_6 \underset{NH}{\overset{NH}{\diagup\diagdown}} Se \underset{NH}{\overset{NH}{\diagup\diagdown}} C_{10}H_6$$
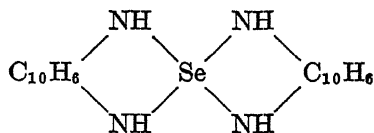
The compound 1,3-dimethyl-2,6-dioxypiaselenolpurine

$$
\begin{array}{cc}
CH_3N\text{—}CO & \\
| \quad\quad | & \\
OC \quad C\text{—}N & \\
\| \quad\quad \| & Se \\
CH_3N\text{—}C\text{—}N &
\end{array}
$$
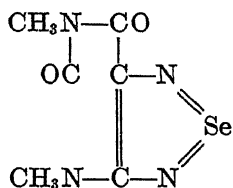
TABLE 1

Reactions with selenium dioxide yielding organic selenium compounds

NAME OF COMPOUND REACTED WITH SeO$_2$	REACTION CONDITIONS	PRODUCTS FORMED	REFERENCES
Amylene....................		Addition compound	(154)
Butadiene	CHCl$_3$; low temperature	No reaction	(9)
Cyclohexene.................		Addition compound	(154)
2,3-Dimethylbutadiene......	CHCl$_3$; low temperature	Cyclic selenone	(9)
3-Chloro-2-methylbutadiene.	CHCl$_3$; low temperature	Cyclic selenone	(9)
2-*tert*-Butylbutadiene	CHCl$_3$; low temperature	Cyclic selenone	(9)
2,3-Di-*tert*-butylbutadiene...	CHCl$_3$; low temperature	Cyclic selenone	(9)
2,3-Diphenylbutadiene..	CHCl$_3$; low temperature	Cyclic selenone	(9)
1,2,3,4-Tetramethyl-butadiene................	CHCl$_3$; low temperature	Unstable product	(9)
2,3-Diethyl-1,4-dimethyl-butadiene................	CHCl$_3$; low temperature	Unstable product	(9)
Camphene...................	Reflux	Camphene selenide	(264)
Benzene....................	Friedel–Crafts synthesis	Diphenyl selenide, diphenyl diselenide, diphenylselenium dichloride, *p*-chlorophenyl selenide	(40, 139)
Toluene....................	Friedel–Crafts synthesis	Tritolylselenonium chloride	(51)
Anisole.....................	Friedel–Crafts synthesis	Trianisylselenonium chloride	(97)
Phenetole..................	Friedel–Crafts synthesis	Triphenetylselenonium chloride	(97)
Resorcinol dimethyl ether ..	Friedel–Crafts synthesis	Mixture of products	(97)
Mercury dialkyls............	50–60°C.	(RHg)$_2$SeO$_3$, R$_2$Se, R$_2$SeO	(155)
Triphenylphosphine.........	C$_6$H$_6$; room temperature	(C$_6$H$_5$)$_3$PSe and (C$_6$H$_5$)$_3$PO	(155)
Triphenylarsine.............	C$_6$H$_6$; room temperature	(C$_6$H$_5$)$_3$AsSe and (C$_6$H$_5$)$_3$AsO	(155)
Triphenylstibine..	C$_6$H$_6$; room temperature	(C$_6$H$_5$)$_3$SbSe and (C$_6$H$_5$)$_3$SbO	(155)
Ethyl bromide...	Grignard synthesis	Ethyl acid selenite	(126)
Methanol....................	Low temperature	Methyl hydrogen selenite	(6)
Methanol...........	<200°C.	Dimethyl selenite	(153)
Ethanol.....................	Low temperature	Ethyl hydrogen selenite	(101)

TABLE 1—*Continued*

NAME OF COMPOUND REACTED WITH SeO₂	REACTION CONDITIONS	PRODUCTS FORMED	REFERENCES
Ethanol	<200°C.	Diethyl selenite	(153)
1-Propanol	<200°C.	Di-*n*-propyl selenite	(153)
1-Butanol	<200°C.	Di-*n*-butyl selenite	(153)
Isobutyl alcohol	<200°C.	Diisobutyl selenite	(153)
Isoamyl alcohol	<200°C.	Diisoamyl selenite	(153)
Isoamyl alcohol and ammonia	Low temperature	Ammonium isoamyl selenite	(52)
Piperidine	Low temperature	Piperidine selenite	(141, 142)
Aniline	Low temperature	Unstable addition compound	(6, 54, 101)
Aniline sulfate	In H₂SO₄	Black crystals	(67)
Methylaniline	Low temperature	Unstable addition compound	(6)
p-Toluidine	Low temperature	Unstable addition compound	(6)
Benzidine and acetone	Low temperature	Ternary addition compound	(72)
Oxalic acid	Steam bath	SeO₂·(COOH)₂	(83)
Oxalic acid	See table 2		
(CH₃)₄NCl		((CH₃)₄NCl)₂·SeO₂	(38)
(C₂H₅)₄NCl		((C₂H₅)₄NCl)₂·SeO₂	(38)
Phenol	H₂SeO₃	(HOC₆H₄)₂Se	(240)
Phenol	In H₂SO₄	Colorless crystals	(67)
Phenoxyacetic acid	H₂SeO₃	(C₆H₄OCH₂COOH)₂SeO	(240)
Resorcinol	H₂SeO₃	Brown powder	(68)
Dimethyldihydroresorcinol	Methanol	Anhydromethon-selenium oxide	(26, 232)
Resorcinolarsonic acid	In H₂SO₄	Colorless product	(67)
β-Naphthol	Ethyl acetate	(HOC₁₀H₆)₂Se	(26)
Salicylic acid	In H₂SO₄	Colorless crystals	(67)
o-Nitrophenol	In H₂SO₄	Yellow product	(67)
p-Nitrophenol	In H₂SO₄	Yellow product	(67)
p-Acetaminophenetidine	In H₂SO₄	(C₂H₅OC₆H₃NHCOCH₃)₃·SeSO₄·H₂O	(67)
Antipyrine	In H₂SO₄	Diantipyryl selenide, (C₁₁H₁₁ON₂)₂Se	(67)
p-Nitroantipyrine	Formic acid	Di-*p*-nitroantipyryl selenide	(68)
p-Tolylantipyrine	Alcohol	Di-*p*-tolylantipyryl selenide	(68)
Ethylhydroquinine	In H₂SO₄	Selenoethylhydro-quinine	(249)
Ethylhydrocupreine	In H₂SO₄	Selenoethylhydro-cupreine	(249)
Hydrocupreine	In H₂SO₄	Selenohydrocupreine	(249)
Tetramethyldiamino-diphenylmethane	In H₂SO₄	Tetramethyl-2,6-di-aminoselenopyronine	(15, 16)

<div align="center">TABLE 1—Continued</div>

NAME OF COMPOUND REACTED WITH SeO₂	REACTION CONDITIONS	PRODUCTS FORMED	REFERENCES
Tetramethyldiaminodiphenyl-methane derivatives.......	In H₂SO₄	Selenopyronines	(17)
o-Phenylenediamine........	Water	Piaselenol	(99, 101)
Carboxy or sulfonic aromatic diamines...........	Water	Piaselenol derivatives	(94)
4-Methyl-1,2-phenylenediamine....	Water	4-Methyl-1,2-piaselenol	(99)
4-Hydroxy-1,2-phenylenediamine.....................	Water	4-Hydroxy-1,2-piaselenol	(75, 94)
1,2-Naphthylenediamine.....	Water and sodium acetate	Naphthylene-1,2-piaselenol	(99)
o-Tolylenediamine...........	In aqueous HCl	Methylchloropiaselenol	(100)
Peri-naphthylenediamine....	In pyridine or methanol	Dihydrodi-peri-naphthoselendiazole	(102)
Peri-naphthylenediamine....	In HCl–CH₃COOH solution	Di-peri-naphthoselendiazole	(102, 214)
o-C₆H₅NHC₆H₄NH₂·HCl.....	Water	Phenylpiaselenazonium chloride	(18)
1,3-Dimethyl-2,6-dioxy-4,5-diaminopyrimidine........	Water	1,3-Dimethyl-2,6-dioxypiaselenolpurine	(215)
Thioglycolic acid...........	Selenite	(HOOCCH₂S)₂Se	(21b)
Cysteine...................		Cysteine–SeO₂ complex	(27, 183)
Cysteine hydrochloride......	Na₂SeO₃	Selenium tetracysteine	(234)
Glutathione................	Selenite	(RS)₂Se compound	(21b)
Dithiocarbamates.......	Alcohol	Selenium dithiocarbamates	(203)
Mold growth................	K₂SeO₃ and bread crumbs	Dimethyl selenide, (CH₃)₂Se	(23)
Mono- and di-butyldecalins.	SeO₂ + Cl₂ + ultraviolet light	Selenium-containing products(?)	(111)
Hydrogen cyanide...........	(CH₃CO)₂O; sealed tube	Se(CN)₂	(101)

has been prepared from 1,3-dimethyl-2,6-dioxy-4,5-diaminopyrimidine and selenious acid by Sachs and Meyerheim (215).

A reaction related to the formation of piaselenols is that reported by Stamm and Gossrau (232), in which dimethyldihydroresorcinol and selenium dioxide produce a compound having a stable six-membered ring, anhydromethonselenium oxide:

$$\text{CH}_2 \text{ -CO—C—SeO—C—CO—CH}_2$$
$$(\text{CH}_3)_2\text{C—CH}_2\text{—}(\qquad -\text{C—CH}_2\text{—C(CH}_3)_2$$
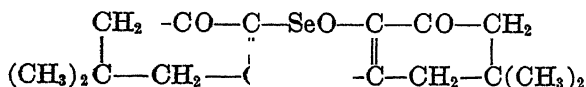
8. Physiological reactions of selenium dioxide

The toxicity of selenium compounds in general has been reviewed satisfactorily in a recent paper by Painter (183). From an industrial viewpoint this

subject has been discussed briefly in a review by one of the authors with Bearse and Shutt (252). For the purposes of this paper it is sufficient to add a few words regarding the toxicology of selenium dioxide.

Selenium dioxide appears to be somewhat more toxic than arsenic trioxide, and the symptoms observed upon ingestion are quite similar to those observed in arsenic poisoning. The animal body reduces selenium dioxide or selenite to harmless selenium, apparently either by the action of sulfur compounds of the tissue proteins or possibly by the glucose carried in the blood stream. The ingestion of selenites into the tissue of live rabbit ears and exposure of the injected region to ultraviolet irradiation causes the tissue to become discolored, owing to the deposition of red selenium. Urban (246) believes this discoloration to be caused largely by the reducing action of the —SH groups of the tissue proteins.

Selenious acid shows a definite corrosive action on the skin upon prolonged contact. Pringle (191) describes the cases of several workers exposed to selenium dioxide and selenious acid in industry who developed rashes or acutely painful paronychia but exhibited no alimentary or other systemic toxic symptoms. Such dermatoses were treated successfully in all but two of about twenty cases by removal of the patient from contact with the selenium compounds, by application of calamine lotion (*British Pharmacopeia*) several times a day, and by the use of ultraviolet irradiation. The wearing of rubber or cotton gloves and long-sleeved overalls is recommended as a protective measure. Any exposed parts should be washed frequently and thoroughly with soap and water. If this last injunction alone is obeyed, the ordinary laboratory worker handling selenium dioxide in small quantities probably never will develop a rash.

9. Analysis of selenium

Methods for the analysis of selenium in various types of compounds are treated adequately in the standard reference works. To complete this review of selenium dioxide reactions it is necessary only to list some of the more recent references pertaining to the analysis of selenium in organic compounds and in the form of selenites.

For the qualitative analysis of selenium in organic compounds Horn (109) suggests digesting 1 g. of the sample with 40 ml. of sulfuric acid and 0.2 g. of mercuric oxide until colorless, cooling, adding sulfuric acid, and testing 5 ml. of this solution with two drops of 3 per cent aqueous codeine sulfate. A green color changing to blue indicates selenium. The quantitative analysis of selenium in various types of organoselenium compounds has been discussed by Silverthorn (226) and by Painter (183).

Adams and Gilberton (1) describe a method for analyzing selenious acid and selenites by oxidizing them to selenate, using standard bromate solution, and determining the excess bromate by titration with standard arsenite solution. Selenium dioxide in air can be determined by the method of Chernyi (42), who suggests that air be passed through water to absorb the selenium dioxide, and the selenium estimated either colorimetrically by reduction with stannous

chloride solution or by the iodine–thiosulfate titration method. Heavy metals can be separated from selenite in alkaline solution by the use of alkaline hydroquinone and sodium sulfite, according to Geilmann and Wrigge (84). The

TABLE 2

Organic reagents used for the qualitative analysis of selenites

NAME OF COMPOUND USED	REACTION CONDITIONS	COLOR OBTAINED	REFERENCES
Pyrrole......................	H_3PO_4–$FeCl_3$	Blue	(20)
Pyrrole......................	Concentrated H_2SO_4	Blue	(213)
Codeine sulfate..............	Concentrated H_2SO_4	Green changing to blue	(109)
Codeine phosphate.........	Concentrated H_2SO_4	Green changing to blue	(192)
Aspidospermine	Concentrated H_2SO_4	Blue-green	(184)
Phenylhydrazine............	Alcohol–water	Red selenium	(90, 174, 188)
as-Diphenylhydrazine.......	Glacial acetic acid	Red to violet	(71)
Phenyl semicarbazide	Alcohol–water	Red selenium	(174)
Polycyclic nitrogen compounds...............	Concentrated H_2SO_4	Various colors	(55)
Thiocyanates..	HCl; hot solution	Red selenium	(93, 114, 136)
Thiourea	Acid solution	Red selenium	(66, 254)
Substituted thioureas........	Acid solution	Red selenium	(255, 260)
Phenolic compounds........	Concentrated H_2SO_4	Various colors	(55, 134)
Acetylene.................	Concentrated H_2SO_4	Red selenium	(118)
Glucose....................	Water	Red selenium	(236)
Rongalite Formaldehyde sulfoxylate....	Acid medium	Red selenium	(244)
Formaldehyde sulfoxylate...	Basic medium	Selenite reduced to colorless selenide	(244)
Oxalic acid	Sunlight, Fe(III)	$H_2SeO_3 + 2FeC_2O_4 + 2H_2C_2O_4 \rightarrow Fe_2(C_2O_4)_3 + 3H_2O + 2CO_2 + Se$	(69a)

conductometric analysis of selenite, using mercurous nitrate, has been studied by Kamecki (124). The equation for the reaction is as follows:

$$Na_2SeO_3 + Hg_2(NO_3)_2 \rightarrow Hg_2SeO_3 + 2NaNO_3$$
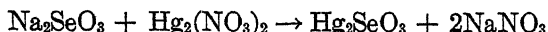
A list of organic reagents that have been suggested for use in spot tests and the qualitative analysis of selenites is given in table 2.

C. LIST OF ORGANIC COMPOUNDS OXIDIZED BY SELENIUM DIOXIDE (TABLE 3)

The compounds listed in table 3 are arranged according to the classification followed in the text of this article.

TABLE 3
List of organic compounds oxidized by selenium dioxide

NAME OF COMPOUND OXIDIZED	REACTION CONDITIONS	PRODUCTS FORMED	REFERENCES
		1. Saturated compounds	
Ethane..................	350–400°C.	Glyoxal, acetic acid, and carbon dioxide	(198)
Alcohols.....................	Low temperature	Alkyl acid selenites	(6, 101, 190, 251)
Alcohols.....................	<200°C.	Dialkyl selenites	(7, 153)
Alcohols.....................	300°C.	Corresponding aldehyde	(153)
Methanol....	400°C.	Water and carbon dioxide	(64)
Ethanol.....................	230°C.	Glyoxal; 5 per cent yield	(7)
Ethanol.....................	400°C.	Water and carbon dioxide	(64)
1-Propanol..................	230°C.	Dialkyl selenite and complex products	(7)
1-Propanol.............	400°C.	Water and carbon dioxide	(64)
1-Butanol..................	230°C.	Dialkyl selenite and complex products	(7)
Tetrahydrofurfuryl alcohol..	Reflux	No reaction	(182)
Menthol................	Alcohol, reflux	Hydroxythymoquinone, thymol, and menthane	(106)
Borneol.....................	Alcohol, reflux	Camphorquinone	(106)
Borneol.....................	Reflux	Camphorquinone; 60 per cent yield	(3)
Isoborneol..................	Alcohol, reflux	Camphorquinone	(106)
Ethylene glycol..............	Reflux	No reaction	(54)
Glycerol.....................	Reflux	No reaction	(54)
Ethyl ether.................	400°C.	Water and carbon dioxide	(64)
Ethyl iodide................	K_2SeO_3	Ethanol	(163)
Formic acid.................	H_2SeO_4	Nothing isolated	(47)
Acetic anhydride...........	Reflux	Glyoxylic acid; 17 per cent yield	(101, 187)
Acetic anhydride........ ...	CH_3COOK at 60°C.	Dihydroxyacetic acid	(193)
Oxalic acid...........	H_2SeO_4	Nothing isolated	(47)
Propionic acid.	Reflux	Pyruvic acid; 2 per cent yield	(54)
Malonic acid................	H_2SeO_4	Nothing isolated	(47)
Gluconic acid...............	Reflux in water	No reaction	(54)
Lauric acid.................	Sealed tube; 300°C.	Undecene	(261)
Myristic acid...............	Sealed tube; 300°C.	Tridecylene	(261)
Palmitic acid...............	Sealed tube; 300°C.	Pentadecene	(261)
Stearic acid................	Sealed tube; 300°C.	Heptadecene	(261)
Ethyl acetate...............	Reflux	Ethyl glyoxalate not obtained	(187)

TABLE 3—*Continued*

NAME OF COMPOUND OXIDIZED	REACTION CONDITIONS	PRODUCTS FORMED	REFERENCES
1. Saturated compounds—*Continued*			
Ethyl lactate................	Reflux	Ethyl 2-keto-3-one-propionate	(8)
Diethyl malonate.	Reflux	Ethyl mesoxalate	(7)
Diethyl malonate	Xylene; 130°C.	Diethyl dihydroxymalonate and monoethyl dihydroxymalonate	(177)
Diethyl succinate....	170°C.	Ethyl hydrogen fumarate and fumaric acid	(7)
Diethyl malate..	Excess ester	Ethyl diketosuccinate and ethyl fumarate	(6)
Diethyl malate.	Excess SeO₂	Ethyl hydrogen mesoxalate and oxalic acid	(6)
Dimethyl tartrate.	Reflux	Methyl fumarate	(8)
Diethyl tartrate.............	Reflux	Ethylketohydroxysuccinate	(8)
Dibutyl tartrate	Reflux	Nothing isolated	(8)
Diamyl tartrate.............	Reflux	Nothing isolated	(8)
2(a) Unsaturated aliphatic compounds			
Acetylene..................	220–240°C.	Carbon dioxide and 6 per cent glyoxal	(198)
Acetylene..................	400°C.	Water and carbon dioxide	(64)
Acetylene..................	Concentrated H_2SO_4	Nothing isolated	(118)
1-Heptyne....		3-Hydroxy-1-heptyne; 27 per cent yield	(242)
1-Heptyne..................	Excess SeO₂	Some $C_4H_9COC\equiv CH$	(242)
1-Octyne..................		3-Hydroxy-1-octyne	(242)
Olefins....................	Selenite catalysts	Glycols and oxides	(68)
Ethylene..................	220–240°C.	Glyoxal; 80 per cent yield	(24, 195, 197, 198)
Ethylene..................	400°C.	Water and carbon dioxide	(64)
Propylene..................	220–240°C.	Methylglyoxal; 19 per cent yield	(198)
Butadiene derivatives.......	Low temperature	Cyclic selenones (see table 1)	(9)
1,3-Pentadiene..............	H_2O_2 + SeO₂	Yields 1,2-diols	(225)
2-Pentene..................	Sealed tube	Complex products	(198)
2-Pentene..................	CH_3COOH + $(CH_3CO)_2O$; 120–140°C.	2-Penten-4-ol	(89)
2-Methyl-2-butene...........	CH_3COOH + $(CH_3CO)_2O$; 120–140°C.	2-Methyl-2-buten-1-ol	(88, 89)

TABLE 3—*Continued*

NAME OF COMPOUND OXIDIZED	REACTION CONDITIONS	PRODUCTS FORMED	REFERENCES
2(a) Unsaturated aliphatic compounds			
Trimethylethylene.....	Benzene	Mechanism of oxidation	(89)
1-Hexene..................	$CH_3COOH + (CH_3CO)_2O$; 120–140°C.	2-Hexen-1-ol and 1-hexen-3(?)-ol	(89)
2-Methyl-2-pentene..........	$CH_3COOH + (CH_3CO)_2O$; 120–140°C.	2-Methyl-2-penten-1-ol	(87, 89)
3-Methyl-2-pentene..........	$CH_3COOH + (CH_3CO)_2O$; 120–140°C.	3-Methyl-3-penten-2-ol	(89)
3-Methyl-2-pentene.........	$CH_3COOH + (CH_3CO)_2O$; 120–140°C.	3-Methyl-3-penten-2-ol	(87, 89)
2,3-Dimethyl-3-pentene......	$CH_3COOH + (CH_3CO)_2O$; 120–140°C.	2-Isopropyl-2-buten-1-ol	(89)
2,2,3-Trimethyl-3-pentene...	$CH_3COOH + (CH_3CO)_2O$; 120–140°C.	2-tert-Butyl-2-buten-1-ol	(89)
3-Nonene...................	$CH_3COOH + (CH_3CO)_2O$; 120–140°C.	Mixture of nonenols	(89)
4-Nonene	$CH_3COOH + (CH_3CO)_2O$; 120–140°C.	Mixture of nonenols	(89)
β-Methylallyl alcohol	Hexyl alcohol or dioxane	β-Methylacrolein; 50–60 per cent yield	(127)
Unsaturated fatty acids....	H_2SeO_3; 100°C.	Double bond preserved	(78)
Oleic acid..................	Benzene under pressure	Double bond preserved	(223)
Castor oil..................	H_2SeO_3; 100°C.	White powder	(78)
Linseed oil.................	Ethanol reflux	Double bonds preserved	(245)
Cottonseed oil..............	Ethanol reflux	Double bonds preserved	(245)
Olive oil...................	Ethanol reflux	Double bonds preserved	(245)
Unsaturated aliphatic-aromatic combinations (see section 2(d)).............			
2(b) Unsaturated alicyclic compounds			
Cyclopentene...............	$(CH_3CO)_2O$ reflux	Cyclopentenol and diol	(53)
Methylcyclopentene........	$(CH_3CO)_2O$; 100°C.	Methylcyclopentenol and methylcyclopentenyl methylcyclopentenone	(53)
Methylcyclopentene........	$CH_3COOH + (CH_3CO)_2O$; 120–140°C.	1-Ethylcyclopenten-5-ol	(89)

TABLE 3—*Continued*

NAME OF COMPOUND OXIDIZED	REACTION CONDITIONS	PRODUCTS FORMED	REFERENCES
2(b) Unsaturated alicyclic compounds—*Continued*			
Cyclopentadiene.......... .	$H_2O_2 + SeO_2$	Yields 1,2-diol	(225)
Cyclohexene	$CH_3COOH +$ $(CH_3CO)_2O$; 120–140°C.	1-Cyclohexen-3-ol	(89)
Cyclohexene......	Alcohol reflux	Cycloölefin ketone	(221–224)
Cyclohexene................	$H_2O_2 + SeO_2$	*trans*-Cyclohexanediol; 45 per cent yield	(225)
1-Methylcyclohexene...... ..	Alcohol reflux or H_2SeO_3 autoclave	Cycloölefin ketone	(221–224)
1-Methylcyclohexane..... ..	Alcohol reflux	1-Methylcyclopenten-6-ol (30–40 per cent ·yield) and some 1-methylcyclopenten-6-one	(247)
1-Methylcyclohexene........	Water reflux	Mostly 1-methylcyclopenten-6-one	(247)
1-Methylcyclohexene...	CH_3COOH reflux	1-Methylcyclopenten-6-ol acetate; 40 per cent yield	(247)
3-Methylcyclohexene..	$CH_3COOH +$ $(CH_3CO)_2O$; 120–140°C.	6-Methylcyclohexanol, 4-methylcyclohexene, 4-methylcyclohexen-3-ol, toluene	(89)
4-Methylcyclohexene.......	$CH_3COOH +$ $(CH_3CO)_2O$; 120–140°C.	4-,5-, and 6-Methylcyclohexen-3-ol, 4-isomer predominating	(89)
1-Ethylcyclohexene.........	$CH_3COOH +$ $(CH_3CO)_2O$; 120–140°C.	1-Ethylcyclohexen-6-ol; 30–40 per cent yield	(88, 89)
1,2-Dimethylcyclohexene ...	$CH_3COOH +$ $(CH_3CO)_2O$; 120–140°C.	First fraction: *o*-xylene and 2,3-dimethyl-1,3-cyclohexadiene Second fraction: one ethylenic and one dienic alcohol	(89)
1,6-Dimethylcyclohexene.....	$CH_3COOH +$ $(CH_3CO)_2O$; 120–140°C.	Five fractions: each containing *o*-xylene and 2,3-dimethyl-1,3-cyclohexadiene	(89)
1,1,4-Trimethylcyclohexene.		Trimethylcyclohexen-5-one	(12)
Δ¹-Menthene................		Carvotanacetone	(25, 221–224)
Δ³-Menthene...............		Δ³-Menthen-5-one	(25, 221–224)
Carvomenthene.............		Carvotanacetone	(239)
α-Phellandrene.............		Cuminaldehyde and *p*-cymene	(25, 104)

TABLE 3—*Continued*

NAME OF COMPOUND OXIDIZED	REACTION CONDITIONS	PRODUCTS FORMED	REFERENCES
2(b) Unsaturated alicyclic compounds—*Continued*			
Dipentene..................		Carvone, *p*-cymene, and *p*-tolyl methyl ketone	(105)
Dipentene		Carvone	(221–224)
2(c) Unsaturated polycarbocyclic compounds			
Indene.....................	Sealed tube; 300°C.	Hydrindene	(261)
Tetralin...................	Reflux or solvents	Bright red *o*(?)-diquinone	(251)
$\Delta^{9,10}$-Octalin................	$(CH_3CO)_2O$; 5°C.	$\Delta^{9,10}$-Octalol-1 acetate	(37)
$\Delta^{9,10}$-Octalin................	$(CH_3CO)_2O$; 30°C.	$\Delta^{9,10}$-Octalindiol-1,5 diacetate	(37)
$\Delta^{9,10}$-Octalin................	$(CH_3CO)_2O$; 120°C.	1,2,3,6,7-Hexahydro-naphthalenediol-1,5 diacetate	(37)
Pinene.....................	Reflux	Myrtenol, myrtanol, β-pinene, and 1,5-pinadiene	(60)
Pinene.....................	Alcohol reflux	Myrtenol, myrtanol	(61)
Pinene.....................		Methyl group in pinene oxidized; some myrtenyl selenide	(264)
α-Pinene..................	Alcohol reflux	Verbenone; 35 per cent yield	(59, 220, 222–224)
β-Pinene..................	Alcohol reflux	Pinocarvone; 35 per cent yield	(59, 222–224)
β-Pinene..................		Pinocarveol and pinocarvone	(265)
β-Pinene..................	Various solvents; SeO_2 in molar ratio	Carvopinone with some pinocarvone	(230)
β-Pinene..................	Alcohol; 0.5 mole SeO_2	Pinocarveol (30 per cent yield); some carvopinone	(117, 231)
β-Pinene.......	CH_3COOH reflux	Pinocarveol; pinocarvyl acetate, carvopinone, and pinocarvone	(231)
Camphene..................	Reflux	Camphene selenide	(264)
Dihydro-α-dicyclo-pentadiene...............	CH_3OH; H_2SeO_3	Methyl ether of dihydro-α-dicyclo-pentadienol	(2)
Dihydro-α-dicyclo-pentadiene...............	C_2H_5OH; H_2SeO_3	Ethyl ether of dihydro-α-dicyclo-pentadienol	(2)

TABLE 3—*Continued*

NAME OF COMPOUND OXIDIZED	REACTION CONDITIONS	PRODUCTS FORMED	REFERENCES
2(c) Unsaturated polycarbocyclic compounds—*Continued*			
Dihydro-α-dicyclo-pentadiene...............	$C_5H_{11}OH$; H_2SeO_3	Amyl ether of di-hydro-α-dicyclo-pentadienol	(2)
Dihydro-α-tricyclo-pentadiene	$(CH_3CO)_2O$; H_2SeO_3	Acetate of dihydro-α-tricyclopentadien-3-ol	(2)
Dihydro-β-tricyclo-pentadiene...............	$(CH_3CO)_2O$; H_2SeO_3	Acetate of dihydro-β-tricyclopentadien-3-ol	(2)
2(d) Aromatic compounds			
Phenol.....................	Low temperature	Tarry resin (however, see table 1)	(54)
o-Cresol....................	Low temperature	Tarry resin	(54)
p-Cresol....................	Low temperature	Tarry resin	(54)
Toluene.	Sealed tube; 300°C.	Benzoic acid; 27.4 per cent yield	(54)
Benzyl alcohol..............	Reflux	Benzaldehyde; approximately 100 per cent yield	(7)
Benzyl chloride.............	Reflux	Benzaldehyde; 49 per cent yield	(76)
Benzyl chloride.............	Reflux	Benzaldehyde and benzoic acid	(163)
p-Nitrobenzyl bromide.......	140–150°C.	p-Nitrobenzaldehyde and benzaldehyde	(76)
p-Nitrobenzyl chloride.......	Alcohol; 140–150°C.	2-Nitrobenzaldehyde; 56 per cent yield	(76)
p-Nitrobenzal bromide.......		p-Nitrobenzoic acid	(76)
2,4-Dinitrotoluene..	Alcohol reflux	No reaction	(76)
2,4,6-Trinitrotoluene........	Alcohol reflux	No reaction	(76)
Styrene.....................	Sealed tube	Nothing isolated	(198)
Styrene.....................	180–250°C.	Phenylglyoxal	(251)
Methylphenylacetylene......	Reflux	Product hydrated in alkaline solution to $C_2H_5COC_6H_5$	(243)
Ethylphenylacetylene........	Reflux	$CH_3CHOHC{\equiv}CC_6H_5$	(243)
3-Phenyl-2-pentene..........	CH_3COOH + $(CH_3CO)_2O$; 120–140°C.	3-Phenyl-3-penten-2-ol	(89)
Eugenol.....................	Benzene; pressure	Double bond in side chain preserved	(223)
Acetisoeugenol..............	Alcohol; 50°C.	Trace of vanillin	(54)
Safrole.....................		α-Ketodihydrosafrole; ethoxysafrole β-Ketodihydrosafrole; piperonylacrolein	(257)

TABLE 3—*Continued*

NAME OF COMPOUND OXIDIZED	REACTION CONDITIONS	PRODUCTS FORMED	REFERENCES
2(d) Aromatic compounds—*Continued*			
Isosafrole.................		Dihydrosafrole, ethoxy-safrole; piperonyl-acrolein	(257)
		A new oxide and a new selenide	
Ethyl phenylacetate........	Reflux	Ethyl benzoylformate; 34 per cent yield	(6)
Ethyl mandelate............	Reflux	Ethyl benzoylformate; 60 per cent yield	(6)
Ethyl β-phenylpropionate....	Reflux	β-Phenylpropionic and cinnamic acids	(6)
5,6-Dimethoxyhomophthalic acid.....................	Xylene	5,6-Dimethoxy-phthalonic acid	(41)
Diphenylmethane..	Reflux	Benzophenone; 87 per cent yield	(187)
Diphenylmethane..........	Reflux	Benzophenone; 47 per cent yield	(76)
4,4′-Dinitrodiphenyl-methane..................	Dioxane	No reaction	(76)
Tolane	280°C.	Benzil; 35 per cent yield	(187)
Stilbene...................		Benzil; 86.6 per cent yield	(6)
Stilbene...................	235°C.	Benzil; 17 per cent yield	(187)
Dibenzyl..................	Sealed tube; 300°C.	Benzil and stilbene	(54)
Dibenzyl		Benzil; 33 and 17.5 per cent yields	(6)
Benzyl *p*-tolyl sulfone.......		No reaction	(48)
2,2-Dimesitylvinyl alcohol...		Mesitil	(82)
Anthracene.................	Melt	Anthraquinone; 76 per cent yield	(187)
Anthracene.................	C₆H₅NO₂	Anthraquinone; 73 per cent yield	(6)
Phenanthrene.......	280°C.	Phenanthraquinone; 3 per cent yield	(187)
Phenanthrene..............		Phenanthraquinone; very little	(6)
Fluorene..................		Fluorenone; 5 per cent yield	(187)
Acenaphthene..............	CH₃COOH; 150–200°C.	Acenaphthylene glycol, acenaphthylene, di-naphthylenecyclo-butane, polyacenaph-thylene	(173)
Triphenylmethane..........	Reflux	Triphenylcarbinol; 15 per cent yield	(76)

TABLE 3—*Continued*

NAME OF COMPOUND OXIDIZED	REACTION CONDITIONS	PRODUCTS FORMED	REFERENCES
	2(d) Aromatic compounds—*Continued*		
Tetraphenylethylene........	220–230°C.	Nothing isolated	(187)
1,1,6,6-Tetraphenyl-1,5-hexadiene................	CH_3COOH and H_2SeO_3	Tetraphenylhexatriene	(218)
1,6-Dibiphenylene-1,5-hexadiene................	CH_3COOH and $C_6H_5OCH_3$	1,6-Dibiphenylene-hexatriene	(218)
Hexaphenylbutyne..........		Nothing isolated	(187)
2-Methyl-1,1'-dinaphthyl ketone...................	$C_6H_5NO_2$ at 230°C.	2-Carboxy-1,1'dinaphthyl ketone	(49)
1,2,5,6-Dibenzfluorene......		1,2,5,6-Dibenzfluorenone	(10)
2-Methylbenzanthrone......	H_2SeO_3; 230–240°C.	Benzanthrone-2-aldehyde	(121–123)
6-Methylbenzanthrone.......	H_2SeO_3; 230–240°C.	Benzanthrone-6-aldehyde	(121–123)
9-Methylmesobenzanthrone .	H_2SeO_3; 230–240°C.	Mesobenzanthrone-9-aldehyde; 20 per cent yield	(50)
10-Methylmesobenzanthrone	$C_6H_5NO_2$; 230-240°C.	Mesobenzanthrone-10-aldehyde; 25 per cent yield	(50)
2-Benzylbenzanthrone.......	H_2SeO_3; 230–240°C.	2-Benzoylbenzanthrone	(121–123)
Indeno-2,3,2,1-benzanthrone....................	H_2SeO_3; 230–240°C.	1″-Ketoindeno-2″,3″, 2′,1′-benzanthrone; 100 per cent	(237)
Dihydro-2,3,2,1-benzanthrone....................	H_2SeO_3; 230–240°C.	1″-Ketoindeno-2″,3″, 2′,1′-benzanthrone	(237)
5-Methylnaphthanthraquinone...................	H_2SeO_3; 230–240°C.	Naphthoanthraquinone-5-carboxaldehyde, naphthoanthraquinone-5-carboxylic acid	(121–123)
1,5-Dibenzoyl-2,6-dimethyl-naphthalene..............	$C_6H_5NO_2$; 230-240°C.	1,5-Dibenzoylnaphthalene-2,6-dicarboxylic acid	(121–123)
	2(e) Complex unsaturated compounds		
Sterols and bile acids:			
Bile acids................		Qualitative test	(35)
Apocholic acid............		β-Dihydroxycholadienic acid	(34)

TABLE 3—*Continued*

NAME OF COMPOUND OXIDIZED	REACTION CONDITIONS	PRODUCTS FORMED	REFERENCES
2(e) Complex unsaturated compounds—*Continued*			
Sterols and bile acids—Cont.: Methylapocholate........		β-Dihydroxycholadienic acid	(34)
Methyl-3(β)-acetoxy-$\Delta^{20,22}$-norallocholenate....	(CH$_3$CO)$_2$O	3(β)-Acetoxy-21-hydroxy-$\Delta^{20,22}$-norallocholenic acid lactone	(210)
3,12-Diketocholanic acid...	CH$_3$COOH; 100°C.	Qualitative test	(235)
Clionastrol...............		4,5-Cliostene-3,6-diol, C$_{29}$H$_{50}$O$_2$	(21)
Cholesterol...............	Se at 230°C.	Cholestanone; 30–40 per cent yield	(56)
Cholesterol...		Two isomeric cholestenediols	(33)
Cholesterol...............		Metacholesterol	(175)
Cholesterol...............	CH$_3$COOH or C$_6$H$_5$NO$_2$	*cis*-$\Delta^{5,6}$-Cholestene-3,4-diol	(202)
Cholesteryl acetate........	CH$_3$COOH	*cis*-$\Delta^{5,6}$-Cholestene-3,4-diol diacetate but mostly *trans*-cholestene-3,4-diol diacetate	(202)
Cholesteryl benzoate......	CH$_3$COOH	*cis*-$\Delta^{5,6}$-Cholestene-3,4-diol (3-benzoate)	(202)
$\Delta^{8,14}$-Cholestene...........	Alcohol reflux	$\Delta^{8,14}$-Cholestadiene	(63)
4-Cholesten-3-one....	CH$_3$COOH; 100°C.	Qualitative test	(235)
4-Cholestene-3,6-dione.. ...	CH$_3$COOH; 100°C.	Qualitative test	(235)
Cholestanone..............	C$_2$H$_5$OH	Cholestan-2,3-dione	(235)
Cholestan-6-one...........	CH$_3$COOH; 100°C.	Qualitative test	(235)
Cholestan-3-ol-6-one......	CH$_3$COOH; 100°C.	Qualitative test	(235)
Cholestane-3,6-dione......	CH$_3$COOH; 100°C.	Qualitative test	(235)
Coprostanone	C$_2$H$_5$OH	Slight reaction	(235)
Ergosterol................		Dehydroergosterol	(35)
Dihydroergosterol........		Dihydroergosterol oxide	(35)
Sitosteryl acetate.........	Benzene	4- and 6-hydroxysitosteryl acetates	(145)
Stigmasteryl acetate..	(CH$_3$CO)$_2$O	4-Hydroxystigmasterol diacetate	(146)
Lanosteryl acetate........	Alcohol	Isomeric diols	(19)
Dihydrolanosteryl acetate.	CH$_3$COOH reflux	Lanosterol acetate	(19)
3'-Keto-4,6-dimethoxy-1,2-cyclopentenonaphthalene.................	CH$_3$COOH reflux	2',3'-Diketo-4,6-dimethoxy-1,2-cyclopentenonaphthalene	(148)

TABLE 3—*Continued*

NAME OF COMPOUND OXIDIZED	REACTION CONDITIONS	PRODUCTS FORMED	REFERENCES
2(e) Complex unsaturated compounds—*Continued*			
Hormones:			
Δ^4-Androsten-17-ol........		Δ^5-Androsten-3-one-17-ol	(228)
Δ^5-Androstene-3,17-diol diacetate...............	H_2SeO_3	Δ^5-Androstene-3,4,17-triol	(144)
Δ^5-Androstene-3,17-diol....	CH_3COOH	Δ^5-Androstene-3,4,17-triol	(144)
trans-Dehydroandrosterone.................		3,4-Dihydroxy-$\Delta^{5,6}$-androsten-17-one and 3,6-dihydroxy-$\Delta^{5,6}$-androsten-17-one	(227)
Δ^5-Pregnene-3,20-diol diacetate...............	CH_3COOH and benzene	Δ^5-Pregnene-3,4,20-triol	(144)
3,17-Dihydroxy-21-oxo-$\Delta^{5,6}$-pregnene...........		$\Delta^{5,6}$-3,4,17,20,21-Pregnenepentol Δ^4-3,6,17,20,21-Pregnenepentol	(227)
Pregnane carbonyl compounds.................		Pregnane polycarbonyl compounds	(164)
Estradiol.................		Cyclopentane ring of estradiol is broken	(108)
Polyterpenes:			
Lupeol...................	Benzene	Lupenol	(116)
Lupeol...................		Lupenalol	(211)
Betulin diacetate.........	CH_3COOH	Diacetoxylupenal	(205)
β-Amyrin acetate.........	CH_3COOH	β-Amyradinenol acetate and β-amyradienedionol acetate	(208)
β-Amyrin acetate.........	Dioxane	β-Amyradinenol acetate and β-amyradienedionol acetate	(208)
β-Amyranonal acetate....		enol-β-Amyranedionol acetate	(206)
β-Amyradienyl-1-acetate...		β-Amyrenonyl acetate and $C_{32}H_{48}O_4$ or $C_{32}H_{46}O_4$	(185)
β-Amyrenonyl acetate.....	CH_3COOH	O_5 acetate	(176)
β-Amyradienonyl acetate..	CH_3COOH	O_5 acetate	(176)

TABLE 3—*Continued*

NAME OF COMPOUND OXIDIZED	REACTION CONDITIONS	PRODUCTS FORMED	REFERENCES
2(e) Complex unsaturated compounds—*Continued*			
Polyterpenes—Cont.:			
β-Amyradienonyl benzoate...............	CH_3COOH	$C_{37}H_{35}O_5$ (O_5 benzoate)	(176)
β-Amyrenonyl benzoate. ..	CH_3COOH	$C_{37}H_{35}O_5$ (O_5 benzoate)	(176)
Isonoragathenol acetate...		Product dehydro- genates to α,β- unsaturated ketone	(204)
Methyl ketoacetylole- anolate.................		$C_{33}H_{46}O_7$	(176)
Methyl acetyldeoxy- glycyrrhetate...........	CH_3COOH	Methyl acetyldehydro- dioxyglycyrrhetate	(22)
Methyl acetyldesoxogly- cyrrhetinate............	CH_3COOH	Methyl acetyldihydro- desoxoglycyrrheti- nate	(207)
Methyl acetyldesoxogly- cyrrhetinate............	Dioxane	Methyl acetyl-β-amyra- dienedionolate	(207)
Miscellaneous:			
Sarsapogenin esters........	CH_3COOH	Halogenated side chain unaffected by SeO_2	(143)
Tetrahydrodiosgenin triacetate...............	CH_3COOH; benzene	Product similar to Δ^5- 3,4-dihydroxychol- estene	(147)
Tetrahydroösajetin tri- methyl ether...........	CH_3COOH	Tetrahydroösajetinone trimethyl ether	(258)
Tetrahydropomiferitin tetramethyl ether........		Tetrahydropomiferi- tone tetramethyl ether	(258)
Abietic acid..............		Dehydroabietic acid	(136a)
3. Aldehydes and ketones			
Aldehydes...................	Kinetics and mechanism of oxidation		(154, 157)
Acetaldehyde...............		Glyoxal; almost 100 per cent yield	(200)
Acetaldehyde...............	CH_3COOH–dioxane	Glyoxal; 72–74 per cent as bisulfite	(201)
Acetaldehyde...............	95 per cent CH_3COOH	Kinetics of oxidation	(157)

TABLE 3—*Continued*

NAME OF COMPOUND OXIDIZED	REACTION CONDITIONS	PRODUCTS FORMED	REFERENCES

3. Aldehydes and ketones—*Continued*

NAME OF COMPOUND OXIDIZED	REACTION CONDITIONS	PRODUCTS FORMED	REFERENCES
Propionaldehyde.............	95 per cent CH_3COOH	Kinetics of oxidation	(157)
Propionaldehyde...........		Methylglyoxal; 30 per cent yield	(200)
Butyraldehyde.............		Ethylglyoxal: 45 per cent yield	(200)
Butyraldehyde.............	95 per cent CH_3COOH	Kinetics of oxidation	(157)
Butyraldehyde acetal.......	95 per cent CH_3COOH	Mechanism of oxidation	(154)
Isobutyraldehyde..	95 per cent CH_3COOH	Mechanism of oxidation	(157)
Heptaldehyde...............	95 per cent CH_3COOH	Mechanism of oxidation	(157)
Crotonaldehyde............	Sealed tube	Nothing isolated	(198)
Crotonaldehyde............	Methanol	β-Methoxy-α-keto-butyraldehyde	(193)
Crotonaldehyde dimethyl acetal....................	Methanol	β-Methoxy-α-keto-butyraldehyde	(193)
Crotonaldehyde............	Ethanol	β-Ethoxy-α-keto-butyraldehyde	(193)
Crotonaldehyde............	$(CH_3CO)_2O$ and H_2SeO_3	β-Acetoxy-α-keto-butyraldehyde	(193)
Crotonaldehyde............	CH_3COOH and H_2SeO_3	Polymeric β-hydroxy-α-ketobutyraldehyde	(193)
Crotonaldehyde............	CH_3COOH (35); $(CH_3CO)_2O$ (65)	Diacetate	(193)
Crotonaldehyde............	CH_3COOH (80); $(CH_3CO)_2O$ (20)	Diacetate and β-acetoxy-α-ketobutyraldehyde	(193)
Crotonaldehyde............	CH_3COOH (95); $(CH_3CO)_2O$ (5)	Diacetate and β-acetoxy-α-ketobutyraldehyde	(193)
Benzaldehyde.............	H_2SeO_4; alcohol	Selenic acid is reduced	(47)
Phenylacetaldehyde........		Phenylglyoxal; 35 per cent yield	(200)
Cinnamaldehyde............	Sealed tube	Nothing isolated	(198)
Cinnamaldehyde............	Sealed tube	Hydrocinnamic acid	(261)
Levulose....................	Acid solution	H_2SeO_3 is reduced easily; glucose, maltose, and lactose show no reaction	(200)
Sucrose.....................	Acid solution	Reduces H_2SeO_3 on prolonged boiling	(200)
Sucrose.....................	H_2SeO_3	Velocity of inversion by H_2SeO_3 studied	(126)

TABLE 3—*Continued*

NAME OF COMPOUND OXIDIZED	REACTION CONDITIONS	PRODUCTS FORMED	REFERENCES
3. Aldehydes and ketones—*Continued*			
Ketones..	.75 per cent CH_3COOH	Kinetics and mechanism of oxidation of the following ketones were studied: acetone; ethyl methyl, methyl propyl, isopropyl methyl, hexyl methyl, diethyl, dipropyl, diisopropyl, dibutyl, methyl phenyl, ethyl phenyl, and propyl phenyl ketones; pinacolone; cyclohexanone; 1,2- 1,3-, and 1,4-methylcyclohexanones	(154, 156)
Ketones....................	Alcohol solvents	Rates of oxidation of acetone, ethyl methyl ketone, and methyl propyl ketone in absolute and aqueous methanol, ethanol, 1-butanol, isobutyl alcohol, and isoamyl alcohol	(158)
Isomeric amyl methyl ketones...................	75 per cent CH_3COOH	Kinetics of oxidation	(160)
Isomeric methyl hexyl ketones...................	75 per cent CH_3COOH	Kinetics of oxidation	(160)
Substituted acetophenones..	75 per cent CH_3COOH	Kinetics of oxidation of m-$NO_2C_6H_4COCH_3$, p-$BrC_6H_4COCH_3$, p-$ClC_6H_4COCH_3$, p-$CH_3OC_6H_4COCH_3$, p-$CH_3C_6H_4COCH_3$, p-$IC_6H_4COCH_3$, and $C_6H_5CH_2COCH_3$	(158)
Acetone.....................	Reflux	Methylglyoxal	(92, 194, 196, 200)
Ethyl methyl ketone........	Reflux	Ethylglyoxal and small amount of diacetyl	(200)
Diethyl ketone.............	Reflux	Ethylmethylglyoxal	(200)
Acetylacetone..............	C_2H_5OH	Triketopentane; 12 per cent yield	(36, 200)
Acetylacetone..............	C_2H_5OH	Triketopentane; 30 per cent yield	(186)

TABLE 3—*Continued*

NAME OF COMPOUND OXIDIZED	REACTION CONDITIONS	PRODUCTS FORMED	REFERENCES
3. Aldehydes and ketones—*Continued*			
Acetonylacetone............		Diacetylethylene; 15 per cent yield	(4)
Ethyl acetonedicarboxylate..		Ethyl α,β-diketobuty-rate	(6)
Ethyl acetoacetate..........	Xylene	Ethyl α,β-diketobuty-rate	(177)
Triacetone mannitol........		Mechanism of oxida-tion	(156)
Pinacolone................		*tert*-Butylglyoxal; 48 per cent yield	(80)
Cyclopentanone.............	Reflux	Cyclopentane-1,2-dione	(200)
Methylcyclopentanone.......	CH_3COOH	Methylcyclopentane-dione	(53)
Cyclohexanone.............	Reflux	Cyclohexane-1,2-dione and some adipic acid	(200)
1-Methyl-4-cyclohexanone....	C_2H_5OH	1-Methyl-3,4-cyclo-hexanedione and 3-ethoxy-Δ^5-cyclo-hexen-4-one	(85)
1-Methyl-3-cyclohexanone...	C_2H_5OH	Similar results	(85)
1-Methyl-2-cyclohexanone..	C_2H_5OH	1-Methyl-Δ^6-cyclo-hexene-2,3-dione	(85)
Cycloheptanone.............	C_2H_5OH	1,2-Cycloheptanedione	(85)
Cycloöctanone	C_2H_5OH	8-Ethoxy-1,2-cycloöc-tanedione	(85)
Acetophenone		Phenylglyoxal	(196, 199, 200)
Propiophenone.............		Phenylmethylglyoxal	(200)
Benzyl methyl ketone.......	C_2H_5OH	Unidentified compound; no $CH_3COCOC_6H_5$	(186)
Acetomesitylene............	Dioxane	Mesitylglyoxal; 82.5 per cent yield	(86)
Benzyl isoduryl ketone......	Dioxane	Isoduryl phenyl dike-tone; 81 per cent yield	(79)
Di(β-isoduryloyl)methane....	Dioxane	Dimesityl triketone	(81)
1,3-Diketohydrindene........	Dioxane	Ninhydrin; 35 per cent yield	(240a)
Isoketopinic acid...........	CH_3COOH	*o*-Oxoisoketopinic acid	(113)
Benzyl phenyl ketone........	$(CH_3CO)_2O$ reflux	Benzil; 86 per.cent yield	(93a)
Benzyl 4-chlorophenyl ketone...................	$(CH_3CO)_2O$ reflux	4-Chlorobenzil; 94 per cent yield	(93a)
Benzyl 4-bromophenyl ketone...................	$(CH_3CO)_2O$ reflux	4-Bromobenzil; 95 per cent yield	(93a)

TABLE 3—*Continued*

NAME OF COMPOUND OXIDIZED	REACTION CONDITIONS	PRODUCTS FORMED	REFERENCES
3. Aldehydes and ketones—*Continued*			
Benzyl *p*-tolyl ketone........	$(CH_3CO)_2O$ reflux	4-Methylbenzil; 75 per cent yield	(93a)
Benzyl *o*-4-xylyl ketone......	$(CH_3CO)_2O$ reflux	3,4-Dimethylbenzil; 95 per cent yield	(93a)
Benzyl *m*-4-xylyl ketone.....	$(CH_3CO)_2O$ reflux	2,4-Dimethylbenzil	(93a)
Benzyl *p*-xylyl ketone.......	$(CH_3CO)_2O$ reflux	2,5-Dimethylbenzil; 90 per cent yield	(93a)
Benzyl mesityl ketone.......	$(CH_3CO)_2O$ reflux	2,4,6-Trimethylbenzil; 92 per cent yield	(93a)
Benzyl 4-diphenylyl ketone..	$(CH_3CO)_2O$ reflux	4-Phenylbenzil; 95 per cent yield	(93a)
2,4,6-Triisopropylaceto-phenone...................	Wet dioxane	2,4,6-Triisopropyl-phenylglyoxal; 82 per cent yield	(81a)
Propiomesitylene...........	Wet dioxane	Mesityl methyl dike-tone; 42 per cent yield	(81a)
3-Nitroacetomesitylene......	Wet dioxane	3-Nitromesitylglyoxal; 72 per cent yield	(81a)
3-Bromoacetomesitylene....	Wet dioxane	3-Bromomesitylglyoxal; 65 per cent yield	(81a)
3-Bromo-5-nitroaceto-mesitylene................	Wet dioxane	3-Bromo-5-nitromesityl-glyoxal; 90 per cent yield	(81a)
Mesityl *p*-nitrobenzyl ketone...................	Wet dioxane	Mesityl *p*-nitrophenyl diketone; 72 per cent yield	(81a)
Mesityl *m*-nitrobenzyl ketone...................	Wet dioxane	Mesityl *m*-nitrophenyl diketone; 81 per cent yield	(81a)
p-Bromobenzyl mesityl ketone.............	Wet dioxane	Mesityl *p*-bromophenyl diketone; 72 per cent yield	(81a)
Menthone...................	C_2H_5OH	Hydroxythymoquinone	(103)
Piperitone		Thymol and oxythymo-quinone	(104)
Camphor....................	$(CH_3CO)_2O$, dioxane	Camphorquinone; 65 per cent yield	(3)
Camphor....................	$(CH_3CO)_2O$; 140–150°C.	Camphorquinone; good yield	(65)
Camphor....................	C_2H_5OH	Camphorquinone; 27 per cent yield	(248)

<div align="center">TABLE 3—Continued</div>

NAME OF COMPOUND OXIDIZED	REACTION CONDITIONS	PRODUCTS FORMED	REFERENCES

<div align="center">3. Aldehydes and ketones—Continued</div>

NAME OF COMPOUND OXIDIZED	REACTION CONDITIONS	PRODUCTS FORMED	REFERENCES
Camphor....................	Toluene or xylene	Camphorquinone; 88–90 per cent yield	(248)
Camphor....................	$(CH_3CO)_2O$	Camphorquinone; 95 per cent yield	(248)
l-Epicamphor...............	$(CH_3CO)_2O$	Camphorquinone	(5)
d-Epicamphor...............	$(CH_3CO)_2O$	Camphorquinone	(5)
α-Hydroxycamphor..........	C_2H_5OH	Camphorquinone; 40 per cent yield	(248)
α-Hydroxycamphor..........	No solvent	Camphorquinone; 85 per cent yield	(248)
α-Chlorocamphor...........	No solvent	Camphorquinone; 30 per cent yield	(248)
α-Bromocamphor...........	No solvent	Camphorquinone; 55 per cent yield	(248)
Ethylcamphor..............	No solvent	Camphorquinone; 12 per cent yield and some ethylene-camphor	(248)
Benzylcamphor..............	No solvent	Benzylidenecamphor; 95 per cent yield	(248)
Isonitrosocamphor...........	85°C.	Camphornitrile (23 per cent) and camphoric anhydride (27 per cent)	(248)
Isonitrosocamphor...........	Alcohol	Camphornitrile (20 per cent) and camphoric anhydride (12 per cent)	(248)
Isonitrosocamphor..........	Toluene	Camphornitrile (36 per cent) and camphoric anhydride (36 per cent)	(248)
4-*p*-Nitrophenylcamphor.....	$(CH_3CO)_2O$	4-*p*-Nitrophenyl-camphorquinone	(179)
2-Methyl-1,4-naphtho-quinone..................	C_2H_5OH	No reaction	(256)
3-Methyl-1-tetralone........	Various alcohols	2-Hydroxy-3-methyl-1,2-naphthoquinone and 3-methyl-1,2-naphthoquinone	(256)
3-Ethyl-5-hydroxy-6,7-di-methoxy-1-tetralone.......	CH_3COOH or alcohol	Red dye formed	(253)
3-Ethyl-5,6,7-trimethoxy-1-tetralone.................	CH_3COOH or alcohol	No dye formation	(253)

TABLE 3—*Continued*

NAME OF COMPOUND OXIDIZED	REACTION CONDITIONS	PRODUCTS FORMED	REFERENCES

4. Nitrogen compounds

See table 1 for a list of amines and other nitrogen compounds that react with SeO₂ to form organic selenium compounds and table 2 for a number of nitrogen compounds used in qualitative tests for selenite

NAME OF COMPOUND OXIDIZED	REACTION CONDITIONS	PRODUCTS FORMED	REFERENCES
Urea	C₂H₅OH and HCl	No reaction	(101)
Leucine	Sealed tube; 300°C.	Unidentified products	(261)
Diazoacetic ester	H₂SeO₃	Selenite reduced in aqueous solution	(126)
o-Aminophenol	Low temperature	Tarry resin	(54)
p-Aminophenol	Low temperature	Tarry resin	(54)
Pyridine (pure)	Reflux	No reaction	(95)
α-Picoline	Reflux	Picolinic acid and aldehyde	(95)
α-Picoline	CH₃COOC₂H₅	Picolinic acid and aldehyde (small yield)	(26)
β-Picoline	Reflux	Nicotinic acid	(95)
β-Picoline	H₂SO₄; 250–330°C.	Nicotinic acid; 50 per cent of theoretical	(259)
2,6-Lutidine		Dipicolinic acid	(95)
Quinoline (pure)	Reflux	No reaction	(95)
Quinoline	H₂SO₄; 250–330°C.	Nicotinic acid; 75 per cent of theoretical	(259)
Quinaldine	Xylene	α-Quinolinealdehyde and acid	(95)
Quinaldine	Xylene	α-Quinolinealdehyde and acid	(170)
Quinaldine	Aged H₂SeO₃	Quinaldoin	(125)
Lepidine	Aged H₂SeO₃	1,2-Di-4-quinolyl-ethylene	(125)
Lepidine	Xylene	Quinoline-4-aldehyde and cinchoninic acid	(130)
Lepidine		Quinoline-4-aldehyde (yield unsatisfactory)	(44)
6-Methoxylepidine	Xylene	6-Methoxyquinoline-4-aldehyde; 52 per cent yield	(130)
8-Nitrolepidine	C₂H₅OH	8-Nitroquinoline-4-aldehyde	(115)
8-Nitrolepidine		No reaction	(128)
2-Ethyl-3-methylquinoline		3-Methyl-2-carboxy-quinoline	(95)
2,3,8-Trimethylquinoline	C₂H₅OH	3,8-Dimethylquino-line-2-aldehyde	(31)
5-Nitro-2,3,8-trimethyl-quinoline	C₂H₅OH	5-Nitro-3,8-dimethyl-quinoline-2-aldehyde	(31)
1-Methylisoquinoline	Dioxane	Isoquinaldehyde; 42 per cent yield	(32)

TABLE 3—*Continued*

NAME OF COMPOUND OXIDIZED	REACTION CONDITIONS	PRODUCTS FORMED	REFERENCES

4. Nitrogen compounds—*Continued*

NAME OF COMPOUND OXIDIZED	REACTION CONDITIONS	PRODUCTS FORMED	REFERENCES
1,3-Dimethyl-6,7-methylene dioxoisoquinoline..........	Dioxane	1,3-Dimethyl-6,7-methylenedioxoiso-quinaldehyde	(32)
Acridine....................	300°C.; sealed tube	Dihydroacridine	(261)
9-Methylacridine...........	Sand bath	9-Acrinaldehyde	(171)
1,2,3,4-Tetrahydroacridine..	$CH_3COOC_2H_5$	Acridine and 4-oxo-tetrahydroacridine	(26)
2-Methyl 3,4-tetrahydro-acridine..................	$CH_3COOC_2H_5$	2-Methylacridine and 2-methyl-4-oxotetra-hydroacridine	(26)
4-Hydroxy-2-methylquina-zoline	CH_3COOH; 50–60°C.	4-Hydroxyquinazoline-2-aldehyde	(172)
2-Methyl-β-naphthoxazole....	Toluene; 90°C.	β-Naphthoxazole-2-aldehyde	(110)
1,2-Dimethylbenzimidazole		1-Methylbenzimidazole 2-aldehyde	(110)
5,6-Benzo-7-azahydrindine..		Benzoazahydrindone	(26)
Nicotine....................	H_2SO_4; 250–330°C.	Nicotinic acid; 75 per cent of theoretical	(259)
Hydroquinine	Xylene	Hydroquininone; 45 per cent yield	(140)
Papaverine.................	CH_3COOH	Papaveraldine	(160a)
Phenylsemicarbazide........	H_2SeO_3	Qualitative test	(174)
Arylhydrazines.............	H_2SeO_3	Qualitative test	(70, 71, 90, 101, 174)
Hydrazones..	H_2SeO_3	Qualitative test	(70)
Osazones..................	H_2SeO_3	Qualitative test	(70)
Phenylhydrazine	C_2H_5OH	Diphenylamine; 94 per cent yield	(188)
Phenylhydrazine.......... .	Acid solution	Tetraphenyltetrazene and blue dye	(188)
Phenylhydrazine hydro-chloride.........	Acid solution	Product coupled with β-naphthol; 60 per cent dye	(188)
α-Naphthylhydrazine hydro-chloride..................	Acid solution	Product coupled with β-naphthol; 25 per cent dye	(188)
β-Naphthylhydrazine hydro-chloride...............	Acid solution	Product coupled with β-naphthol; 40 per cent dye	(188)

TABLE 3—*Continued*

NAME OF COMPOUND OXIDIZED	REACTION CONDITIONS	PRODUCTS FORMED	REFERENCES

4. Nitrogen compounds—*Continued*

m-Nitrophenylhydrazine hydrochloride	Acid solution	Product coupled with β-naphthol; 80 per cent dye	(188)
p-Nitrophenylhydrazine.....	Acid solution	*p*-Nitrophenyltriazine and p-$NO_2C_6H_4N=$ $NNHC_6H_4NO_2$-p	(188)

5. Sulfur compounds

See tables 1 and 2 for a list of sulfur compounds that react with selenium dioxide to form organic selenium compounds or are used in the qualitative analysis of selenite

Thiocyanate ion.	Acid solution	Se(s), CN^-, S^-, and H_2O	(136)
Thiocyanate ion..	Acid solution	Se(s), NH_4^+, SO_4^{--}, S, and CO_2	(93)
Thiodiglycol.	$CaCl_2$–SeO_2	Red selenium produced on moistening with water	(28)
β,β'-Dichlorodiethyl sulfide.	$CaCl_2$–SeO_2	Red selenium produced on moistening with water	(28)
Phenylmercaptan	H_2SeO_3	Phenyl disulfide and organic selenium compounds	(101)
2-Hydroxythianaphthene....	C_2H_5OH at 0°C.	Isothioindigo	(42a)
Thiourea	C_2H_5OH	Bis(aminoiminomethyl) disulfide	(254)
Substituted thioureas........ Compounds giving test include methyl-, allyl-, diethyl-, trimethyl-, phenyl-, benzyldiethyl-, dimethylphenyl-thioureas; thioacetamide; and thiobenzamide Tetrasubstituted thioureas do not react	C_2H_5OH	Qualitative test for —SH group in organic compounds	(255)
Substituted thioureas..... ..	H_2SeO_3	Qualitative test	(260)

Thioureas giving red color or precipitate: allyl-, di-*n*-butyl-, phenyl-, benzyl-, *o*-tolyl-, *p*-tolyl-, *p*-hydroxyphenyl-, *p*-fluorophenyl-, *p*-methoxyphenyl-, *p*-ethoxyphenyl-, *o*-*n*-butyloxyphenyl-, α-naphthyl-, di-*o*-hydroxycyclohexyl-, *N*-(β-hydroxyethyl)-*N'*-isoamyloxyphenyl-, *N*-methyl-*N'*-4-ethoxyphenyl-, and *N*-ethyl-*N'*-4-isobutyloxyphenyl-.

Thioureas giving pink color or precipitate: monolauryl-, *s*-diethyl-, 2,4-dimethylphenyl-, *ac*-tetrahydro-β-naphthyl-, phenylethanol-, *s*-di-*o*-tolyl-, *N*-4-ethoxyphenylpiperidyl-, *N*-(β-hydroxyethyl)-*N'*-4-allyloxyphenyl-, *N*-dimethyl-*N'*-4-ethoxyphenyl-, and *N*-(*n*-butyl)-*N'*-4-ethoxyphenyl-.

Thioureas giving yellow color or precipitate: *m*-tolyl-, xylidyl-, *s*-diphenyl-, *s*-di-*m*-tolyl-, phenyl-*o*-tolyl-, *p*-isoamyloxyphenyl-, dimethylcyclohexyl-, *N*-dimethyl-*N'*-4-isopropyloxyphenyl-, *N*-(di-*n*-butyl)-*N'*-4-ethoxyphenyl-, *N*-(*p*-chlorophenyl)-*N'*-acetyl, and *N,N'*-di(*p*-hydroxyphenyl)-; also *m*-phenylene- and *p*-phenylene-dithioureas.

TABLE 3—*Continued*

NAME OF COMPOUND OXIDIZED	REACTION CONDITIONS	PRODUCTS FORMED	REFERENCES

6. Oxidations with SeO_2 in concentrated sulfuric acid

Many organic compounds react with selenium dioxide to form organic selenium compounds, as shown in table 1; reactions of analytical interest are listed in table 2

Carbon monoxide............	Effect of catalysts and temperature on the oxidation to CO_2		(165–167)
Carbon oxysulfide......	Effect of catalysts and temperature on the oxidation to CO_2		(166)
Ethylene...............	Effect of catalysts and temperature on the oxidation to CO_2		(166)
Sucrose	Effect of catalysts and temperature on the oxidation to CO_2		(166)
Diphenylamine............	SeO_2–H_2SO_4	Cornflower-blue color	(137)
Pyrrole.............	SeO_2–H_2SO_4	Blue color	(20, 213)
Codeine....................	SeO_2–H_2SO_4	Blue-green color	(109)
Codeine phosphate..........	SeO_2–H_2SO_4	Blue-green color	(192)
Aspidospermine..............	SeO_2–H_2SO_4	Blue-green color	(184)
Alkaloids.	SeO_2–H_2SO_4	Color reactions	(30, 57, 73, 109, 118, 131, 133, 149, 151, 181a, 184, 217)
β-Picoline	SeO_2–H_2SO_4	See Section 4 (oxidation of nitrogen compounds)	
Quinoline....................	SeO_2–H_2SO_4	See Section 4 (oxidation of nitrogen compounds)	
Nicotine......	SeO_2–H_2SO_4	See Section 4 (oxidation of nitrogen compounds)	
Nitrogen compounds........	SeO_2–H_2SO_4	Color reactions	(55)

Compounds that produce colors are: o-aminodiphenyl, p-aminodiphenyl, 4-aminodiphenylamine, benzeneazodiphenylamine, aniline, p-bromoaniline, m-chloroaniline, carbanilide, diphenylamine, 2,4-diaminodiphenylamine, dibenzylaniline, di-2-naphthylamine, diphenylbenzidine, formyldiphenylamine, methyldiphenylamine, 4-nitrodiphenylamine, o-toluidine hydrochloride, p-toluidine hydrochloride, tolidine, 1-naphthylamine, 2-naphthylamine, s-diphenylethylenediamine, s-dimethylcarbanilide, diphenylcarbamine hydrochloride, s-diphenylcarbazide, s-diphenylcarbazone, 4,5-diphenylglyoxalone, diphenylpiperazine, 1,4-diphenylsemicarbazide, 4,4-diphenylsemicarbazide, p-nitrophenylhydrazine, l-leucine, cholesterol, carbanilide, tryptophan, triphenylguanidine, cysteine hydrochloride, di-p-phenetylurea, s-di-o-tolylurea, s-di-m-tolylurea, s-di-p-tolylurea, s-di-o-tolylthiourea, s-di-p-tolylthiourea, phenylthiourea, thiocarbanilide, methylthiocarbanilide, and diphenylthiocarbazide.

Compounds giving either a faint pink or no color at all: ethylamine hydrobromide, ethylenediamine, 2-propanolamine, triethanolamine, tri-2-propanolamine, morpholine, hexamethyleneamine, dimethylaniline, diethylaniline, o-chloroaniline, p-chloroaniline,

TABLE 3—*Concluded*

NAME OF COMPOUND OXIDIZED	REACTION CONDITIONS	PRODUCTS FORMED	REFERENCES

6. Oxidations with SeO_2 in concentrated sulfuric acid—*Continued*

methylaniline, *n*-nitroaniline, tribenzylamine, hydroxylamine hydrochloride, guanidine hydrochloride, diphenylguanidine, di-*o*-tolylguanidine, *o*-, *m*-, and *p*-aminobenzoic acids, *p*-dimethylaminobenzaldehyde, sulfanilic acid, urea, phenylurea, *s*-diethylcarbanilide, thiourea, allylthiourea, phenylhydrazine, pyridine, α-picoline, quinoline, glycine, *l*-cystine, *dl*-α-amino-α-methylbutyric acid, *l*-proline, *l*-oxyproline, *dl*-serine, *dl*-valine, *dl*-isoleucine, asparagine, creatinine, *d*-arginine hydrochloride, β-phenylalanine, diiodotyrosine, barbituric acid, and phenobarbital.

Compounds giving same color as in concentrated sulfuric acid alone: methyl-*o*-, methyl-*m*-, and methyl-*p*-toluidines, dibenzylamine, *o*- and *m*-bromoanilines, *p*-nitroaniline, *m*- and *p*-phenylenediamines, benzidine, *p,p'*-diaminodiphenylmethane, *p*-nitrosodiphenylamine, diphenylnitrosamine, and diphenylthiocarbazone.

Phenolic compounds.. ......| SeO_2–H_2SO_4 | Color reactions | (134)

The following compounds were tested: phenol, amidol, anisole, phenetole, phenacetin, acetylsalicyclic acid, cresols, salicylaldehyde, methyl and phenyl salicylates, pyrocatechol, guaiacol, vanillin, vanillic acid, piperonol, resorcinol, hydroquinone, pyrogallol, phloroglucinol, eugenol, thymol, carvacrol, α and β- naphthols, chrysarobin; the glucosides arbutin and phloridzin; the alkaloids morphine, heroin, dionine, narcotine, narceine, and papaverine; the dyes orcein, alizarin, and purpurin. Mono-, di-, and trinitrophenols do not produce colors; phenolic aldehydes and acids give only faint colors. Cholesterol plus acetic anhydride in SeO_2–H_2SO_4 yields a fleeting purple going over to red.

VII. REFERENCES

(1) ADAMS, D. F., AND GILBERTSON, L. I.: Ind. Chem. Eng., Anal. Ed. **14,** 926 (1942).
(2) ALDER, K., AND STEIN, G.: Ann. **504,** 205 (1933).
(3) ALLARD, J.: Bull. inst. pin. **2,** 727 (1934).
(4) ARMSTRONG, K. F., AND ROBINSON, R.: J. Chem. Soc. **1934,** 1650.
(5) ASAHIMA, Y., ISHIDATE, M., AND MOMOSE, T.: Ber. **67,** 1432 (1934).
(6) ASTIN, S., MOULDS, L. DE V., AND RILEY, H. L.: J. Chem. Soc. **1935,** 901.
(7) ASTIN, S., NEWMAN, A. C. C., AND RILEY, R. L.: J. Chem. Soc. **1933,** 391.
(8) ASTIN, S., AND RILEY, H. L.: J. Chem. Soc. **1934,** 833.
(9) BACKER, H. J., AND STRATING, J.: Rec. trav. chim. **53,** 1113 (1934).
(10) BADGER, G. M.: J. Chem. Soc. **1941,** 535.
(11) BAKER, R. H., AND MAXSON, R. N.: *Inorganic Syntheses,* Vol. 1, p. 119.   John Wiley and Sons, Inc., New York (1939).
(12) BARBIER, H.: Helv. Chim. Acta **23,** 531, 1477 (1940).
(13) BARNES, E.: J. Indian Chem. Soc. **9,** 329 (1932).
(14) BARNES, E.: J. Indian Chem. Soc. **12,** 22 (1935).
(15) BATTEGAY, M., AND HUGEL, G.: Bull. soc. chim. **27,** 557 (1920).
(16) BATTEGAY, M., AND HUGEL, G.: Bull. soc. chim. **31,** 440 (1922).
(17) BATTEGAY, M., AND HUGEL, G.: Bull. soc. chim. **33,** 1103 (1923).
(18) BATTEGAY, M., AND VECHOT, J.: Bull. soc. chim. **37,** 1271 (1925).
(19) BELLAMY, L. J., AND DOREE, C.: J. Chem. Soc. **1941,** 176.
(20) BERG, R., AND TEITELBAUM, M.: Mikrochemie, Emich Festschrift, p. 23 (1930).
(21) BERGMANN, W., AND KIND, C. A.: J. Am. Chem. Soc. **64,** 473 (1942).
(21a) BERGSTROM, F. W.: Chem. Rev. **35,** 120, 186 (1944).
(21b) BERSIN, T.: Ergeb. Enzymforsch. **4,** 68 (1935).

(22) BILHAM, P., KON, G. A. R., AND ROSS, W. C. J.: J. Chem. Soc. **1942,** 535.
(23) BIRD, M. L., AND CHALLENGER, F.: J. Chem. Soc. **1939,** 163.
(24) BLACET, F. E., AND MOULTON, R. W.: J. Am. Chem. Soc. **63,** 868 (1941).
(25) BORGWARDT, E., AND SCHWENK, E.: J. Am. Chem. Soc. **56,** 1185 (1934).
(26) BORSCHE, W., AND HARTMANN, H.: Ber. **73B,** 839 (1940).
(27) BORSOOK, H., ELLIS, E. L., AND HUFFMAN, H. M.: J. Biol. Chem. **117,** 281 (1937).
(28) BRADLEY, T. F.: Chem. Eng. News **20,** 893 (1942).
(29) BRADSTREET, R. B.: Chem. Rev. **27,** 331 (1940).
(30) BRANDT, C.: Jahresber. Pharm., p. 341 (1875).
(31) BURGER, A., AND MODLIN, L. R., JR.: J. Am. Chem. Soc. **62,** 1081 (1940).
(32) BURROWS, R. S., AND LINDWALL, H. G.: J. Am. Chem. Soc. **64,** 2430 (1942).
(33) BUTENANDT, A., AND HAUSMANN, E.: Ber. **70,** 1154 (1937).
(34) CALLOW, R. K.: J. Chem. Soc. **1936,** 462.
(35) CALLOW, R. K., AND ROSENHEIM, O.: J. Chem. Soc. **1933,** 387.
(36) CALVIN, M., AND WOOD, C. L.: J. Am. Chem. Soc. **62,** 3152 (1940).
(37) CAMPBELL, W. P., AND HARRIS, G. C.: J. Am. Chem. Soc. **63,** 2721 (1941); **64,** 720 (1942).
(38) CARNEVALI, F.: Atti accad. Lincei [5] **17,** ii, 385 (1908).
(39) CARTER, S. R., BUTLER, J. A. V., AND JAMES, F.: J. Chem. Soc. **1926,** 930.
(40) CHABRIE, C.: Bull. soc. chim. [3] **2,** 788 (1889).
(41) CHAKRAVARTI, S. M., AND SWAMINATHAN, M.: Current Sci. **2,** 472 (1934).
(42) CHERNYI, M. E.: Trudy i Materialy Sverdlov. Inst. Eksptl. Med. **1940,** No. 4, 175.
(42a) CHOVIN, P.: Compt. rend. **215,** 419 (1942).
(43) CLARK, C. W. (to Canadian Copper Refiners Ltd.): U. S. patent 2,322,348 (June, 1943).
(44) CLEMO, G. R., AND HOGGARTH, E.: J. Chem. Soc. **1939,** 1241.
(45) DE CONINCK, W. O.: Compt. rend. **142,** 571 (1906).
(46) DE CONINCK, W. O., AND CHAUVENET, E.: Bull. acad. roy. Belg. **1906,** 51.
(47) DE CONINCK, W. O., AND CHAUVENET, E.: Bull. acad. roy. Belg. **1906,** 601.
(48) CONNOR, R., FLEMING, C. L., JR., AND CLAYTON, T.: J. Am. Chem. Soc. **58,** 1386 (1936).
(49) COOK, J. W.: J. Chem. Soc. **1932,** 1472.
(50) COPP, F. C., AND SIMONSEN, J. L.: J. Chem. Soc. **1942,** 209.
(51) CROWELL, J. H., AND BRADT, W. E.: J. Am. Chem. Soc. **55,** 1500 (1933).
(52) CURTIS, H. A., AND BURNS, R. M.: J. Am. Chem. Soc. **39,** 33 (1917).
(53) DANE, E., SCHMITT, J., AND RAUTENSTRAUCH, C.: Ann. **532,** 29 (1937).
(54) DEUPREE, J. F., AND LYONS, R. E.: Proc. Indiana Acad. Sci. **46,** 101 (1937).
(55) DEWEY, B. T., AND GELMAN, A. H.: Ind. Eng. Chem., Anal. Ed. **14,** 361 (1942).
(56) DOREE, C., AND PETROW, V. A.: J. Chem. Soc. **1935,** 1391.
(57) DRAGENDORFF, J. G.: Z. Chem. [2] **2,** 3 (1866).
(58) DREYFUS, H.: French patent 770,420 (September, 1934).
(59) DUPONT, G., ALLARD, J., AND DULOU, R.: Bull. soc. chim. **53,** 599 (1933).
(60) DUPONT, G., AND ZACHAREWICZ, W.: Compt. rend. **200,** 759 (1935).
(61) DUPONT, G., ZACHAREWICZ, W., AND DULOU, R.: Compt. rend. **198,** 1699 (1934).
(62) DUPONT, R.: Ind. chim. belge **10,** 307 (1939).
(63) ECK, J. C., AND HOLLINGSWORTH, E. W.: J. Am. Chem. Soc. **64,** 140 (1942).
(64) EMELEUS, H. J., AND RILEY, H. L.: Proc. Roy. Soc. (London) **A140,** 378 (1933).
(65) EVANS, W. C., RIDGEON, J. M., AND SIMONSEN, J. L.: J. Chem. Soc. **1934,** 137.
(66) FALCIOLA, P.: Ann. chim. applicata **17,** 261 (1927).
(67) FARBWERKE VORM. M. L. G. B.: German patent 299,510 (1917).
(68) FARBWERKE VORM. M. L. G. B.: German patents 348,906 and 350,376 (1918).
(69) FARMER, E. H.: Trans. Faraday Soc. **38,** 347 (1942); J. Chem. Soc. **1942,** 124.
(69a) FEIGL, F.: J. Chem. Education **22,** 36 (1945).
(70) FEIGL, F., AND DEMANT, V.: Mikrochim. Acta **1,** 134 (1937). *Cf.* FEIGL, F., AND DEMANT, V.: *Spot Tests,* pp. 321-5. Nordemann Publishing Company, Inc., New York (1943).

(71) FEIGL, F., AND DEMANT, V.: Mikrochim. Acta 1, 322 (1937).
(72) FEIGL, F., AND FEIGL, E.: Z. anorg. allgem. Chem. 20, 357 (1931).
(73) FERREIRA DA SILVA, A. J.: Compt. rend. 112, 1266 (1891).
(74) FIRTH, J. B., AND GETHING, H. H.: J. Chem. Soc. 1936, 633.
(75) FISCHER, E. (to Bayer and Co.): U. S. patent 1,074,425 (September, 1913); Swiss patent 62,686 (February, 1913).
(76) FISHER, C. H.: J. Am. Chem. Soc. 56, 2056 (1934).
(77) FISHER, C. H., AND EISNER, A. J.: J. Org. Chem. 6, 169 (1941).
(78) FOKIN, S. A.: J. Russ. Phys. Chem. Soc. 45, 285 (1913).
(79) FUSON, R. C., ARMSTRONG, M. D., WALLACE, W. E., AND KNEISLEY, J. W.: J. Am. Chem. Soc. 66, 1274 (1944).
(80) FUSON, R. C., GRAY, H., AND GOUZA, J. J.: J. Am. Chem. Soc. 61, 1937 (1939).
(81) FUSON, R. C., MATUSZESKI, J. F., AND GRAY, A. R.: J. Am. Chem. Soc. 56, 2100 (1934).
(81a) FUSON, R. C., AND SOPER, A. F.: J. Org. Chem. 9, 193 (1944).
(82) FUSON, R. C., SOUTHWICK, P. L., AND ROWLAND, S. P.: J. Am. Chem. Soc. 66, 1109 (1944).
(83) GASSMANN, T.: Z. physiol. Chem. 100, 209 (1917).
(84) GEILMANN, W., AND WRIGGE, F. W.: Z. anorg. allgem. Chem. 210, 357 (1933).
(85) GODCHOT, M., AND CAUQUIL, G.: Compt. rend. 202, 326,444 (1936).
(86) GRAY, A. R., AND FUSON, R. C.: J. Am. Chem. Soc. 56, 739 (1934).
(87) GUILLEMONAT, A.: Compt. rend. 201, 904 (1935).
(88) GUILLEMONAT, A.: Compt. rend. 200, 1416 (1935).
(89) GUILLEMONAT, A.: Ann. chim. 11, 143 (1939).
(90) GUTBIER, A.: Z. anorg. Chem. 32, 257 (1902).
(91) HAGISAWA, H.: Bull. Inst. Phys. Chem. Research (Tokyo) 18, 648 (1939).
(92) HAHN, G., AND SCHALES, O.: Ber. 67, 1823 (1934).
(93) HALL, W. T.: Ind. Eng. Chem., Anal. Ed. 10, 395 (1938).
(93a) HATT, H. H., PILGRIM, A., AND HURRAN, W. J.: J. Chem. Soc. 1936, 93.
(94) HEINEMANN, F.: German patent 261,412 (February, 1912); British patent 3042 (February, 1913).
(95) HENZE, M.: Ber. 67, 750 (1937).
(96) HENZE, M., AND HENZE, C.: German patent 697,759 (September, 1940).
(97) HILDITCH, T. P., AND SMILES, S.: J. Chem. Soc. 93, 1384 (1908).
(98) HILL, A. E., SOTH, G. C., AND RICCI, J. E.: J. Am. Chem. Soc. 62, 2719 (1940).
(99) HINSBERG, O. Ber. 22, 863, 866, 2897 (1889).
(100) HINSBERG, O. Ber. 23, 1393 (1890).
(101) HINSBERG, O. Ann. 260, 40 (1890); Ber. 24, 5 (1891).
(102) HINSBERG, O. Ber. 52B, 21 (1919).
(103) HIRAYAMA, S. J. Chem. Soc. Japan 58, 1393 (1937).
(104) HIRAYAMA, S. J. Chem. Soc. Japan 59, 67 (1938).
(105) HIRAYAMA, S. J. Chem. Soc. Japan 59, 229 (1938).
(106) HIRAYAMA, S. J. Chem. Soc. Japan 59, 683 (1938).
(107) HIRAYAMA, S. Chem. Rev. (Japan) 5, 134 (1939).
(108) HOLWEG, W., AND HERLOFF, H. (to Schering A.-G.): German patent 705,862 (April, 1941).
(109) HORN, M. L.: Ind. Eng. Chem., Anal. Ed. 6, 34 (1934).
(110) I. G. Farbenindustrie A.-G.: French patent 847,527 (October, 1939).
(111) I. G. Farbenindustrie A.-G.: French patent 842,509 (June, 1939).
(112) ISHIKAWA, F., AND ABE, H.: Sci. Papers Inst. Phys. Chem. Research (Tokyo) 34, 775 (1938).
(113) ISIDATE, M., KAWAKATA, H., AND MAKAGAWA, K.: Ber. 74B, 1707 (1941).
(114) IVANOV, W. N.: Chem.-Ztg. 32, 468 (1908).
(115) JOHNSON, O. H., AND HAMILTON, C. S.: J. Am. Chem. Soc. 63, 2864 (1941).
(116) JONES, E. R. H., AND MEAKINS, R. J.: J. Chem. Soc. 1941, 757.
(117) JOSHEL, L. M., AND PALKIN, S.: J. Am. Chem. Soc. 64, 1008 (1942).

(118) JOUVE, A.: Bull. soc. chim. [3] **25**, 489 (1901).
(119) JULIEN, A. P.: Bull. soc. chim. **47**, 1799 (1925).
(120) JUNG, W.: Anales soc. cient. argentina **132**, 201 (1941).
(121) KACER, K. (to I. G. Farbeindustrie A.-G.): German patent 557,249 (December, 1929).
(122) KACER, K. (to I. G. Farbenindustrie A -G.): British patent 347,743 (October, 1930).
(123) KACER, K. (to General Aniline Works, Inc.): U. S. patent 1,935,949 (November, 1933).
(124) KAMECKI, J.: Roczniki Chem. **19**, 433 (1939).
(125) KAPLAN, H.: J. Am. Chem. Soc. **63**, 2654 (1941).
(126) KARVE, D. D.: J. Indian Chem. Soc. **2**, 128 (1925).
(127) KAUTTER, C. T. (to Rohm and Haas Co.): U. S. patent 2,171,727 (September, 1939).
(128) KRAHLER, S. E., AND BURGER, A.: J. Am. Chem. Soc. **64**, 2417 (1942).
(129) KRATZL, K.: Österr. Chem. Ztg. **41**, 340 (1938).
(130) KWARTLER, C. E., AND LINDWALL, H. G.: J. Am. Chem. Soc. **59**, 524 (1937).
(131) LAFON, P.: Compt. rend. **100**, 1543 (1885).
(132) LATIMER, W. M.: *Oxidation Potentials*, pp. 64–81. Prentice-Hall, Inc., New York (1938).
(133) LAURO, M. F.: Ind. Eng. Chem., Anal. Ed. **3**, 401 (1931).
(134) LEVINE, V. E.: J. Lab. Clin. Med. **11**, 809 (1926); Science [2] **52**, 207 (1920).
(135) LINSTEAD, R. P.: Annual Reports of the Chemical Society **34**, 238 (1937).
(136) LJUNG, H. A.: Ind. Eng. Chem., Anal. Ed. **9**, 328 (1937); J. Elisha Mitchell Sci. Soc. **53**, 229 (1937).
(136a) LOMBARD, R.: Compt. rend. **213**, 793 (1941); Fette u. Seifen **50**, 377 (1943).
(137) LUNGE, G.: Ber. **20**, 2032 (1887).
(138) LU VALLE, J. E., AND SCHOMAKER, V.: J. Am. Chem. Soc. **61**, 3521 (1939).
(139) LYONS, R. E., AND BRADT, W. E.: Ber. **60**, 60 (1927).
(140) McKEE, R. L., AND HENZE, H. R.: J. Am. Chem. Soc. **66**, 2022 (1944).
(141) MARINO, L., AND SQUINTANI, V.: Atti accad. Lincei **20**, II, 666 (1911).
(142) MARINO, L., AND TONINELLI, A.: Atti accad. Lincei **21**, II, 98 (1912).
(143) MARKER, R. E. (to Parke Davis and Co.): U. S. patent 2,352,849 (July, 1944).
(144) MARKER, R. E., CROOKS, H. M., AND WITTBECKER, E. L.: J. Am. Chem. Soc. **63**, 777 (1941).
(145) MARKER, R. E., KAMM, O., AND WITTLE, E. L. J. Am. Chem. Soc. **60**, 1071 (1938).
(146) MARKER, R. E., AND ROHRMANN, E.: J. Am. Chem. Soc. **60**, 1073 (1938).
(147) MARKER, R. E., AND TURNER, D. L.: J. Am. Chem. Soc. **63**, 769 (1941).
(148) MARTIN, R. H., AND ROBINSON, R.: J. Chem. Soc. **1943**, 491.
(149) MARTINI, A.: Univ. nacl. litoral (Rosario, Argentina) **3**, 5 (1939).
(150) MAYOR, Y.: Chimie & industrie **43**, 188 (1940).
(151) MECKE, P.: Z. öffentl. Chem. **5**, 351 (1899).
(152) MELNIKOV, N. N.: Uspekhi Khim. **5**, 443 (1936).
(153) MELNIKOV, N. N., AND ROKITSKAYA, M. S.: J. Gen. Chem. (U.S.S.R.) **7**, 1532 (1937).
(154) MELNIKOV, N. N., AND ROKITSKAYA, M. S.: J. Gen. Chem. (U.S.S.R.) **7**, 2738 (1937).
(155) MELNIKOV, N. N. AND ROKITSKAYA, M. S.: J. Gen. Chem. (U.S.S.R.) **8**, 834 (1938).
(156) MELNIKOV, N. N., AND ROKITSKAYA, M. S.: J. Gen. Chem. (U.S.S.R.) **8**, 1369 (1938).
(157) MELNIKOV, N. N., AND ROKITSKAYA, M. S.: J. Gen. Chem. (U.S.S.R.) **9**, 1158 (1939).
(158) MELNIKOV, N. N., AND ROKITSKAYA, M. S.: J. Gen. Chem. (US.S.R.) **9**, 1808 (1939).
(159) MELNIKOV, N. N., AND ROKITSKAYA, M. S.: J. Gen. Chem. (U.S.S.R.) **10**, 1439 (1940).
(160) MELNIKOV, N. N., AND ROKITSKAYA, M. S.: J. Gen. Chem. (U.S.S.R.) **10**, 1713 (1940).
(160a) MENON, K. N.: Proc. Indian Acad. Sci. **19A**, 21 (1944).
(161) MEYER, JL.: Ber. **55B**, 2082 (1922).
(162) MEYER, JL., AND JANNEK, J.: Z. anorg. Chem. **83**, 62 (1913).
(163) MICHAELIS, A., AND LANDMANN, B.: Z. anorg. Chem. **13**, 656 (1880).
(164) MIESCHER, K., AND WETTSTEIN, A. (to Ciba Co.): U. S. patents 2,323,276 and 2,323,277 (June, 1944).
(165) MILBAUER, J.: Z. Elektrochem. **41**, 594 (1935); *cf.* Chem Obzor. **11**, 208 (1936); **12**, 17 (1937); **16**, 97 (1941).

(166) MILBAUER, J.: Chem. Obzor. **11**, 1, 65, 132, 183, 233 (1936).
(167) MILBAUER, J.: Chem. Obzor. **14**, 233 (1939); **16**, 1 (1941).
(168) MILBAUER, J.: Chem. Obzor. **15**, 145 (1940).
(169) MILBAUER, J., AND MIKOLASEK, J.: Chem. Obzor. **15**, 65, 84 (1940).
(170) MONTI, L.: Atti accad. Lincei **18**, 505 (1933).
(171) MONTI, L.: Atti accad. Lincei **24**, 145 (1936).
(172) MONTI, L.: Atti accad. Lincei **28**, 96 (1938).
(173) MONTI, L.: Atti X° congr. intern. chim. **3**, 256 (1939).
(174) MONTIGNIE, E.: Bull. soc. chim. **51**, 127 (1932).
(175) MONTIGNIE, E.: Bull. soc. chim. [5] **1**, 290 (1934).
(176) MOWER, M., GREEN, J., AND SPRING, F. S.: J. Chem. Soc. **1944**, 256.
(177) MÜLLER, R.: Ber. **66B**, 1668 (1933).
(178) NAESER, C. R.: *Inorganic Syntheses*, Vol. 1, p. 117. John Wiley and Sons, Inc., New York (1939).
(179) NAMETKIN, S. S., AND SHEREMAT'EVA, T. V.: Compt. rend. acad. sci. U.R.S.S. **38**, 131 (1943).
(180) NAVES, Y. R., AND IGOLEN, M. G.: Bull. inst. pin. **1935**, 234.
(181) OLSON, O. E., AND JENSEN, C. W.: Proc. S. Dakota Acad. Sci. **20**, 115 (1940).
(181a) ORLOFF, N. A.: Chem.-Ztg. **25**, 66 (1901).
(182) PAILLARD, H., AND SZASZ, R.: Helv. Chim. Acta **26**, 1856 (1943).
(183) PAINTER, E. P.: Chem. Rev. **28**, 179 (1941).
(184) PALET, L. P. J.: Ann. chim. anal. **23**, 25 (1918).
(185) PICARD, C. W. AND SPRING, F. S.: J. Chem. Soc. **1941**, 35.
(186) PIUTTI, P.: Gazz. chim. ital. **66**, 276 (1936).
(187) POSTOVSKII, J. YA., AND LUGOVKIN, B. P.: Ber. **68B**, 852 (1935).
(188) POSTOVSKII, J. YA., LUGOVKIN, B. P., AND MANDRYK, G. T.: Ber. **69B**, 1913 (1936).
(189) PRASAD, M., AND DHARMATTI, S. S.: Proc. Indian Acad. Sci. **12A**, 185 (1940).
(190) PRIDEAUX, E. B. R., AND GREEN, G.: J. Phys. Chem. **28**, 1273 (1924).
(191) PRINGLE, P.: Brit. J. Dermatol. Syphilis **54**, 54 (1942).
(192) RAIKHINSTEIN, Tz.: Trans. Inst. Pure Chem. Reagents (U.S.S.R.) **6**, 27 (1927).
(193) RAPPEN, L.: J. prakt. Chem. **157**, 177 (1941).
(194) RILEY, H. L. (to Imperial Chemical Industries Ltd.): British patent 354,798 (February, 1930).
(195) RILEY, H. L. (to Imperial Chemical Industries Ltd.): British patent 376,306 (July, 1932).
(196) RILEY, H. L. (to Imperial Chemical Industries Ltd.): U. S. patent 1,955,890 (April, 1934).
(197) RILEY, H. L. (to Imperial Chemical Industries Ltd.): U. S. patent 1,999,576 (April, (1935).
(198) RILEY, H. L., AND FRIEND, N. A. C.: J. Chem. Soc. **1932**, 2342.
(199) RILEY, H. L., AND GRAY, A. R.: *Organic Syntheses*, Vol. 15, p. 67. John Wiley and Sons, Inc., New York (1935).
(200) RILEY, H. L., MORLEY, J. F., AND FRIEND, N. A. C.: J. Chem. Soc. **1932**, 1876.
(201) RONZIO, A. R., AND WAUGH, T. D.: *Organic Syntheses*, Vol. 24, p. 61. John Wiley and Sons, Inc., New York (1944).
(202) ROSENHEIM, O., AND STARLING, W. W.: J. Chem. Soc. **1937**, 377.
(203) RUSSELL, W. F. (to R. T. Vanderbilt Co., Inc.): U. S. patent 2,347,128 (April, 1944).
(204) RUZICKA, L., AND BERNOLD, E.: Helv. Chim. Acta **24**, 1167 (1941).
(205) RUZICKA, L., BRENNER, M., AND REY, E.: Helv. Chim. Acta **25**, 161 (1942).
(206) RUZICKA, L., AND JEGER, O.: Helv. Chim. Acta **24**, 1178 (1941).
(207) RUZICKA, L., AND JEGER, O.: Helv. Chim. Acta **25**, 775 (1942).
(208) RUZICKA, L., JEGER, O., AND NORYMBERSKI, J.: Helv. Chim. Acta **25**, 457 (1942).
(209) RUZICKA, L., AND PLATTNER, PL. A.: Helv. Chim. Acta **20**, 809 (1937).
(210) RUZICKA, L., PLATTNER, PL. A., AND PATAKI, J.: Helv. Chim. Acta **25**, 425 (1942).
(211) RUZICKA, L., AND ROSENKRANZ, G.: Helv. Chim. Acta **23**, 2311 (1940).

(212) SA, A.: Rev. centro estud. farm. bioquím. **27,** 19, 48 (1937).
(213) SACCARDI, P., AND MARTINI, G.: Chim. ind. agr. biol. **13,** 210 (1937).
(214) SACHS, F.: Ann. **365,** 150 (1909).
(215) SACHS, F., AND MEYERHEIM, G.: Ber. **41,** 3957 (1908).
(216) SADOVSKII, P. I.: Zavodskaya Lab. **8,** No. 10–11, 1184 (1939).
(217) SCHMIDT, E.: Arch. Pharm. **252,** 161 (1914).
(218) SCHMITT, J.: Ann. **547,** 103 (1941).
(219) SCHOTT, H. F., SWIFT, E. H., AND YOST, D. M.: J. Am. Chem. Soc. **50,** 721 (1928).
(220) SCHWENK, E., AND BORGWARDT, E.: Ber. **65B,** 1601 (1932).
(221) SCHWENK, E., AND BORGWARDT, E. (to Schering-Kahlbaum A.-G.): German patent 582,545 (August, 1933).
(222) SCHWENK, E., AND BORGWARDT, E. (to Schering-Kahlbaum A.-G.): British patent 403,838 (1933).
(223) SCHWENK, E., AND BORGWARDT, E. (to Schering-Kahlbaum A.-G.): French patent 751,807 (September, 1933).
(224) SCHWENK, E., AND BORGWARDT, E. (to Schering-Kahlbaum A.-G.): German patent 584,373 (September, 1933).
(225) SEGUIN, P.: Compt. rend. **216,** 667 (1943).
(225a) SERGEEFF, M. P.: Russ. Pharm. J. **36,** 431 (1897).
(226) SILVERTHORN, R. W.: Chemist-Analyst **30,** 52, 62 (1941).
(227) SOCIÉTÉ POUR L'INDUSTRIE CHIMIQUE À BÂLE: Swiss patents 212,336 and 212,337 (March, 1941).
(228) SOCIÉTÉ POUR L'INDUSTRIE CHIMIQUE À BÂLE: British patent 550,683 (January, 1943).
(229) SREENIVASAN, A., AND SADISIVAN, V.: Ind. Eng. Chem., Anal. Ed. **11,** 314 (1939).
(230) STALLCUP, W. D., AND HAWKINS, J. E.: J. Am. Chem. Soc. **63,** 3339 (1941).
(231) STALLCUP, W. D., AND HAWKINS, J. E.: J. Am. Chem. Soc. **64,** 1807 (1942).
(232) STAMM, H., AND GOSSRAU, K.: Ber. **66B,** 1558 (1933).
(233) STEIN, G.: Angew. Chem. **54,** 146 (1941).
(234) STEKOL, J. A.: J. Am. Chem. Soc. **64,** 1742 (1942).
(235) STILLER, E. T., AND ROSENHEIM, O.: J. Chem. Soc. **1938,** 353.
(236) STOLBA, F.: Z. anal. Chem. **11,** 437 (1872).
(237) SWAIN, G., AND TODD, A. R.: J. Chem. Soc. **1942,** 626.
(238) TABOURY, M. F., AND QUEUILLE, J.: Compt. rend. **217,** 150 (1943).
(239) TABUTEAU, J.: Compt. rend. **200,** 244 (1935).
(240) TAKAMATSU, M.: J. Pharm. Soc. (Japan) **48,** 450 (1928).
(240a) TEETERS, W. O., AND SHRINER, R. L.: J. Am. Chem. Soc. **55,** 3026 (1933).
(241) TREADWELL, W. D., AND FRÄNKEL, E.: German patent 279,005 (December, 1913).
(242) TRUCHET, R.: Compt. rend. **196,** 706 (1933).
(243) TRUCHET, R.: Compt. rend. **196,** 1613 (1933).
(244) TSCHUGAJEW, L., AND CHLOPIN, W.: Ber. **47,** 1269 (1914).
(245) TURK, A., DAWSON, J. W., AND SOLOWAY, S.: Am. Paint J. **28,** 16, 18, 20 (1943).
(246) URBAN, G.: Arch. exptl. Path. Pharmakol. **202,** 337 (1943).
(247) URION, E.: Compt. rend. **199,** 363 (1934).
(248) VENE, J.: Compt. rend. **216,** 772 (1943).
(249) VEREINIGTE CHININFABRIKEN ZIMMER & CIE, G. M. B. H.: German patent 331,145 (December, 1920).
(250) WAGENMAN, K. (to Mansfeldscher Kupferschieferbergbau A.-G.): German patent 700,497 (November, 1940).
(251) WAITKINS, G. R.: Unpublished observations.
(252) WAITKINS, G. R., BEARSE, A. E., AND SHUTT, R.: Ind. Eng. Chem. **34,** 899 (1942).
(253) WALLENFELS, K.: Ber. **74B,** 1428 (1941).
(254) WERNER, A. E. A.: Analyst **65,** 286 (1940).
(255) WERNER, A. E. A.: Sci. Proc. Roy. Dublin Soc. **22,** 387 (1941).

(255a) WEYGAND, C.: Beiheft Z. Ver. Deut. Chem. No. 45; Die Chemie 55, 60 (1942).

(256) WEYGAND, F., AND SCHRÖDER, K.: Ber. 74B, 1844 (1941).

(257) WIERZCHOWSKI, P.: Roczniki Chem. 16, 451 (1936).

(258) WOLFRAM, M. L., AND MAHAN, J.: J. Am. Chem. Soc. 64, 311 (1942).

(259) WOODWARD, C. F., BADGETT, C. O., AND KAUFMAN, J. G.: Ind. Eng. Chem. 36, 544 (1944).

(260) YOE, J. H., AND OVERHOLSER, L. G.: Ind. Eng. Chem., Anal. Ed. 14, 435 (1942).

(261) YOKOYAMA, M.: J. Chem. Soc. Japan 59, 262, 271 (1938).

(262) YOST, D. M., AND HATCHER, J. B.: J. Am. Chem. Soc. 54, 151 (1932).

(263) YOST, D. M., AND RUSSELL, H., JR.: Systematic Inorganic Chemistry, pp. 318, 345. Prentice-Hall, Inc., New York (1944).

(264) ZACHAREWICZ, W.: Roczniki Chem. 16, 290 (1936).

(265) ZACHAREWICZ, W.: Roczniki Chem. 17, 630 (1937).

THE SULFUR DYES

W. NORTON JONES, JR.

Fort Lewis Branch, Colorado State College, Hesperus, Colorado

CONTENTS

I. INTRODUCTION

Members of the class of tinctorial materials known as the sulfur dyes are numerous and have been widely used for many years, yet, since their compositions and structures remain unknown, no precise definition of the generic term is possible. In a general way the sulfur dyes may be said to be a group of organic compounds which are prepared by heating various nitrogenous organic starting materials with sulfur, sodium sulfide, sodium polysulfide, or other sulfurating agents. The products of such processes are mixtures of sulfur-containing compounds of high molecular weight and low solubility. Pure compounds susceptible of specific characterization have not yet been separated from these mixtures.

Most important of the properties common to the individual members of the class is their ability to serve as vat dyes for cotton. They may be applied to the fiber from baths containing sodium sulfide or hydrosulfite and produce quite fast shades of yellow, brown, blue, violet, and black.

The meager information concerning the structure of the sulfur dyes indicates that the sulfur is present in thiazine rings, thiazole rings, mercaptan groups, and polysulfide linkages. The sulfur dyes may be related to the thiazole dyes (such as the primulines) and the thionine dyes (such as methylene blue or the thioindigos), since it is possible that they are formed by the further sulfuration of compounds containing the ring systems characteristic of these dyes.

It is the purpose of the present review to collect and present as much pertinent information as possible concerning the sulfur dyes. Indicating as it does the paucity of precise chemical information relative to these compounds, this survey establishes clearly the need for further fundamental research in this field of dye chemistry.

II. A BRIEF RÉSUMÉ OF THE HISTORY OF SULFUR DYES

So far as is known, the first of the sulfur dyes was prepared in the year 1861 when Troost, by reducing a crude mixture of 1,5- and 1,8-dinitronaphthalenes

with sodium polysulfide and other reducing agents, obtained substances which in general contained sulfur and which gave reddish, violet, and blue shades on textile fibers (78). Since these substances had little success as dyes, the sulfur dye industry is more properly dated from 1873, when Croissant and Bretonnière observed that the product obtained by melting organic substances with either alkali sulfides or sulfur and sodium hydroxide dyed cotton fibers directly very fast shades which varied with the conditions of the fusion from grayish brown to black. These dyes, which were known as Cachou de Laval (39), were prepared in the main from material resulting from the vital processes of animals and plants and from certain industrial wastes. Among the starting materials employed may be listed humus, moss, blood, horn, animal excrements, sawdust, gums, tanning materials, and carbohydrates, including sugars, starches, paper, and other forms of cellulose. Two different procedures were employed by these workers: By the first of them the starting material was warmed with an aqueous solution of sodium polysulfide, and dyes yielding lilac and gray shades on cotton were obtained. The reaction involved seemed to be one of addition, since no hydrogen sulfide was evolved during the preparation. By the second process the starting material was heated with sodium polysulfides at 100–300°C. for some hours, during which treatment a considerable quantity of hydrogen sulfide was evolved. This latter process was the more important of the two, for by it the first single dye of any importance, Cachou de Laval Brown, was prepared. It was observed that the higher the temperatures employed in this process, the deeper the shade of the dye obtained. Research on the nature of these dyes was undertaken by Witt (84), but his findings are controversial.

Twenty years passed without further developments of any importance in the field, until in 1893 Vidal discovered that by heating benzene and naphthalene derivatives with sulfur alone, or with sulfur and alkalies, there were produced dyes which not only dyed unmordanted cotton directly, but also withstood decomposition on the fiber (7). This discovery was the turning point in the history of sulfur dye chemistry, for it opened up new and unlimited possibilities and instigated great activity in the field.

Shortly after taking his first patent on a sulfur color, Vidal developed a process for the preparation of the fast black dye known as Vidal Black, which does not render a pure tone on the fiber and which does require fixing, but which has been extremely valuable (8). Following this discovery it was found that the acyl derivatives of nitramines and diamines would yield sulfur colors of yellow and brownish yellow hues which were medium fast (9). The examination of a wide variety of organic compounds as starting materials for sulfur dyes proceeded forthwith.

In 1897 Kalischer advanced the industry considerably by the discovery of Immedial Black, a direct dye of great fastness and beauty, which he obtained by heating hydroxydinitrodiphenylamine with sulfur and sodium sulfide (10). The value of this find lay not alone in the inherent virtue of this one dye, but in the fact that through it a whole series of valuable direct black dyes was made possible. It was also during this year that sulfur monochloride (S_2Cl_2) was used for the first time as a sulfurating agent for organic molecules in the preparation of sulfur

dyes (11). As a result of its use a whole series of black dyes was produced from aminophenol, its homologs, and its derivatives. The next year introduced the thiosulfates of the alkali metals as thionating agents in a patent taken by the Clayton Company for the preparation of a black dye from nitrosophenol (12).

With the exception of a few sulfur dyes which yielded yellowish shades, those obtained prior to 1900 were all very dark in color. Thus it was that the discovery in that year of Immedial Pure Blue (13), which gave very fast, bright, methylene blue shades on cotton, marked another high point in the history of these compounds. Its preparation by heating for a number of hours at 110–115°C. a mixture of sulfur, sodium sulfide, and a base made by the reduction of phenol and dialkyl-p-phenylenediamine suggested further investigations which soon produced a number of similar compounds.

The period from 1900 to 1902, inclusive, saw the greatest activity in sulfur dye chemistry that has yet occurred. A host of organic compounds were examined as possible starting materials for the preparation of such dyes, and many new dyes of various colors, natures, and conditions of preparation were made as a direct result of these investigations. Reference to the dye patents shows that the processes of commercial value developed during this period far exceed in number those of any other period of equal length (43). From January 1, 1900 to July 1, 1902, there appeared an average of two patents per week. For the most part these were filed by the large manufacturing concerns (44) and may be divided into two groups: those involving the preparation of only a single new product, and those patenting a wide variety of similar starting materials whose future use might possibly be of value (57).

As yet it has not been possible to prepare bright red sulfur dyes, but varying shades of violet, purple, and maroon have been obtained by the thionation of certain of the red dyestuffs such as the azines, safranines, rosindulines, and certain of the red azo dyes, sometimes in the presence of copper or copper salts (14). Some of the simpler diphenylamine derivatives also yield reddish dyes (79). The first of these reddish dyes was patented by Cassella and Company on very nearly the same day that Immedial Pure Blue was patented (15). Through the years there has been no marked progress in the preparation of better red sulfur colors. Schwalbe succeeded in preparing some brighter shades up to a yellowish red, and in some measure increased the fastness of these colors (74); but as a whole they are less fast than the browns and blacks obtained from the same series of starting materials.

A greenish sulfur dye was prepared in 1896 by the polysulfide fusion of p-nitro- or p-amino-phenol, or their ethers, in the presence of copper sulfate (16), but a true green was not obtained until 1901 when the sodium sulfonate of the indophenol from p-aminodimethylaniline and phenol was fused with sodium polysulfide in the presence of copper sulfate (17). By a similar treatment of diamines a number of green dyes have since been prepared; many of these have better properties than their prototype.

From Vidal's discovery of his previously mentioned Thiocatechin[1] until 1902,

---

[1] Thiocatechin is the name that Vidal gave to the dyes which he prepared by heating acetylated aromatic diamines and other acetylated aromatic compounds with sulfur alone.

some advances were made in the realm of the yellow, orange, and lighter brown shades (18), but they were few in number. In the latter year, however, it was found that dyes of these shades could be made by the thionation with sulfur alone of toluylene-2,4-diamines or of their acyl and other derivatives (19). These dyes, which are soluble in aqueous solutions of sodium sulfide, resemble the thiazole coloring matters in that they are formed from aromatic compounds containing methyl groups and other non-aromatic substituents. Indeed, the side chains are the most important features of the starting materials, for it has been shown that not only the shade, but also the color, of the resulting dye is dependent upon them (75).

One of the most important advances in the sulfur color industry came in 1908 with the discovery of Hydron Blue and its homologs. Because these dyes may be applied as vat dyes, because they give a fine deep blue tone to cotton, and because they are extremely fast to light, scouring, and bleaching agents they are of especial commercial value and are strong rivals of indigo. These Hydron blues are prepared by the polysulfide fusion of indophenols from carbazole, either with or without the presence of copper salts (20). It is worthy of note that in these processes carbazole finds its first important application in the synthetic dye industry (76).

New sulfur colors are prepared from time to time, but since 1908 there has been a gradual decline in the activity within the field. In 1930 Palmer and Lloyd (69) announced the preparation of a new series of sulfur dyes. They stated that almost any volatile organic compound will yield a reproducible sulfur color when its vapor is passed into molten sulfur maintained at 380°C., but it seems doubtful that all of the products so obtained are sulfur dyes in the accepted sense of that term. These colors were applied in a sodium sulfide bath. Haynn (50) has reported the preparation of a new series of Immedial leuco dyes.

As cheap cotton colors of considerable merit many of these sulfur dyes are in great demand and are manufactured in large quantities by several companies, but they are still prepared by pragmatically determined variations of the original empirical methods. The manufacturers, of course, maintain some research work in the field, but this concerns itself largely with the development of occasional new dyes, the standardization of tinctorial properties, the development of greater fastness in their products, the attainment of greater economy of preparation, and other points similar in nature.

III. TYPES OF ORGANIC COMPOUNDS WHICH YIELD SULFUR DYES

Organic substances exclusively serve as starting materials for the preparation of the sulfur dyes. With the exception of the Cachou de Laval dyes, prepared from a wide variety of plant and animal material, and of those reported by Palmer and Lloyd as prepared from aliphatic substances, the dyes of this class are derived largely from aromatic compounds of the benzene and naphthalene series. Aside from certain mixtures, and from dyes of other classes employed in a few instances, these single aromatic starting materials may be grouped, according to the mother substances of which they are derivatives, into five main

classes: (*a*) benzene, (*b*) naphthalene, (*c*) diphenylamine-nitrated derivatives, (*d*) diphenylamine-indophenols and indamines, and (*e*) azine (58).

The benzene derivatives used are substitution products wherein from one to the entire six of the hydrogens have been replaced by groups which are, for the most part, small. These substituent groups are in a majority of cases NH_2, NO_2, NO, OH, and the smaller alkyl groups, and any combination of these groups. The carboxyl and sulfonic acid groups are also among the common substituents. A number of dyes are prepared from ureas and thioureas which contain as substituents the benzene ring or substituted benzene rings.

The number of patents (43) involving naphthalene derivatives not contained in indo bodies, although moderately large, is not quite so large as the number requiring the use of benzene derivatives. Of those employed the majority are compounds which contain the substituents listed in the preceding paragraph. It must be noted, however, that sulfonic acids of naphthalene are much more prominent than are those of benzene. A number of naphthalene condensation products also find rather wide application as starting materials. While compounds having double nuclei are being discussed, it should also be pointed out that various derivatives of diphenylmethane give rise to a few important dyes of the family. Carbazole and anthracene are polynuclear compounds whose derivatives are also employed. The former is the parent substance of the Hydron dyes, while the latter, as its nitrated, halogenated, and alkylated derivatives, supplies the starting material for various dyes which yield black and reddish shades on the fiber (21).

By far the most important of the parent substances whose derivatives serve as starting materials for the preparation of the sulfur colors is diphenylamine. As has already been pointed out, its derivatives are most conveniently divided into two groups: one containing those of the hydroxydinitrodiphenylamine type; the other containing those of the leuco-quinone-imide type. The nitro derivatives of diphenylamine result from the condensation of halonitrobenzene or halonitronaphthalene compounds, or their sulfonic acids, with aromatic amino compounds. Upon reduction of the nitro group of these condensation products they change into colorless, easily oxidized diphenylamine derivatives. The condensation of the halomononitro compounds proceeds readily if a small quantity of iodine or cupric iodide be added to the reaction mixture (22); if, however, the halonitro compound is to react readily without outside help the halogen atom must have considerable mobility, which is the case if it is present with at least two nitro groups, or with a nitro group and a sulfonic acid group (6). This is especially true if the two necessary groups are in positions which are ortho and para to the halogen atom. The condensation takes place according to the following scheme:
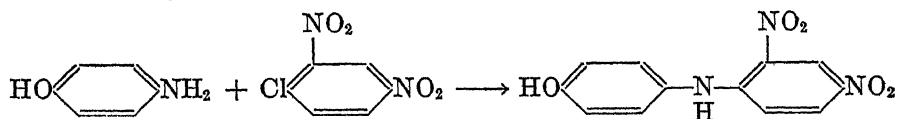
The products of such condensations are easily obtained in crystalline form.

Other halogenated nitro compounds also form condensation products in a very similar fashion. The dihalonitro compounds are used to a moderate extent, and those which have the halogen atoms replaced with hydroxyl, mercapto, and thiocyanate groups are also used occasionally. The sulfonic acids of halonitrobenzenes with aminophenols and similar compounds also yield condensation products of value in the fabrication of sulfur dyes. On reduction these latter condensation products usually yield sundry aminohydroxysulfinic acids.

The indophenol and indamine derivatives of diphenylamine of the type of the leuco-quinone-imide dyestuffs are very important in the commercial preparation of sulfur dyes, and are obtained from the oxidation of aromatic amines together with phenols or still other amines. That the para positions of both of the uniting rings bear either hydroxyl or amino groups is a condition of the reaction. These indo compounds are usually obtained in crystalline form and are unstable in the presence of a variety of reagents which decompose them into quinone and p-diamines. The indophenols frequently undergo further condensation to form phenol ethers. Indophenols which serve for the preparation of green and blue dyes can be formed by the oxidation of naphthalene derivatives with aminophenols (23). Tri- and tetra-phenyl-di- or tri-amine derivatives will also condense with nitrophenol to yield indophenols. The mono- and di-imides of quinone yield indophenols from which a number of good blue sulfur dyes are prepared.

Certain indophenols when treated with neutral sulfites are converted to their water-insoluble sulfonic acid derivatives (24). If these same indophenols be treated with a bisulfite, instead of a sulfite, isomeric water-soluble sulfonic acid derivatives are generated (25). The thiosulfonic acid derivatives can also be prepared, and they find considerable use in industry. Compounds of this variety that are used by the Clayton Company are the di- and tetra-thiosulfonic acids obtained by the oxidation in the presence of sodium thiosulfate of para-substituted benzene derivatives and the subsequent conversion of the oxidation products into indo bodies. The most easily isolated di- and tetra-thiosulfonic acids are those of p-phenylenediamine. On account of their solubility and their extreme susceptibility to oxidation, the thiosulfonic acids of p-aminophenol, hydroquinone, and other similar substances which contain hydroxyl groups cannot be isolated, and therefore can only be assumed to be analogous to those of p-phenylenediamine. The only condition which these starting thiosulfonic acid bodies must fulfill is that upon oxidation they be converted into substances having quinoid linkages. Certain blue dyes of the Badische Anilin und Soda Fabrik are prepared from the indophenols obtained from the quinonethiosulfonic acids.

The azine class of organic starting materials for the sulfur dyes is relatively small and includes three types of derivatives: (a) thiazine, (b) phenazine, and (c) naphthazine. The phenazine division includes the safranines and safraninones, while the members of the naphthazine division are all rosinduline derivatives.

Besides these five general classes of organic starting materials there are also

various and sundry mixtures, as well as a number of single substances, which
yield sulfur colors; these, however, are relatively few and of such widely differing
natures that it is almost impossible to classify them.   The majority of the mix-
tures are composed of two or more members of the foregoing groups.   A few
dyes of other classes—azo, etc.—upon sulfuration yield sulfur colors, as do the
naphthazarin derivatives and certain condensation products of unknown
constitution.

Palmer and Lloyd (69) report that practically any organic compound which
can be vaporized will yield sulfur dyes when the vapors are passed into molten
sulfur at 380°C.   As starting materials they have used a wide variety of aliphatic
and aromatic hydrocarbons and their derivatives, but it hardly seems likely that
many of the products obtained are sulfur dyes as that term is usually construed.

From this discussion it is immediately obvious that the number and variety of
compounds which yield sulfur dyes are very large.

IV. METHODS FOR PRODUCING SULFUR DYES

The methods of sulfurating organic compounds to produce sulfur dyes are
few in number and present very few technical difficulties.   A survey of the
patent literature (43) reveals that a number of sulfurating media are employed;
the most common of these is alkaline polysulfide, while pure pulverized sulfur is
a none too close second.   Fusion in either an open or a closed pot and refluxing
with a solvent are the commonest procedures described.

As was previously stated, alkaline polysulfide fusion was the process employed
by Croissant and Bretonnière in the production of their Cachou de Laval.   This
method, with variations of course, has continued to be the most widely used
procedure for preparing the sulfur colors.   The term "polysulfide" naturally
covers a wide range of possible compositions, the use of any particular one of
which is dependent upon the compound to be sulfurated and the result desired.
This latter matter is more properly the concern of the next section of this paper,
where it will be discussed.   The usual method of preparing the polysulfide
is to melt together sodium sulfide and flowers of sulfur, though sodium hydroxide
and flowers of sulfur may be used.   The following table (59) gives the proportions
of the constituents corresponding to various polysulfide formulas:

$$Na_2S_2 = 240 \text{ parts of } Na_2S + 32 \text{ parts of sulfur}$$
$$Na_2S_3 = 240 \text{ parts of } Na_2S + 64 \text{ parts of sulfur}$$
$$Na_2S_4 = 240 \text{ parts of } Na_2S + 96 \text{ parts of sulfur}$$
$$Na_2S_5 = 240 \text{ parts of } Na_2S + 128 \text{ parts of sulfur}$$
$$Na_2S_6 = 240 \text{ parts of } Na_2S + 160 \text{ parts of sulfur}$$

It is said, however, that alkaline sulfides which possess more sulfur than is
permitted by the formula Na_2S_4 contain the excess as a mechanical mixture (52).
Be that as it may, however, the most stable and the most frequently used in the
preparation of these dyes is the tetrasulfide.

Sulfuration by this method may be effected either by introducing the organic
material into the molten polysulfide or by adding it to the proper quantities of
sulfur and sodium sulfide, after which the fusion is begun.   Experience has shown

that better results are obtained by employing the sulfurating medium in excess of the theory. The sulfuration may proceed in an open pot and is completed when the mass has become dry; it may proceed in a closed pot under pressure with, or without, the presence of solvents such as water, alcohol, or glycerol; or it may proceed by long refluxing either with or without the addition of a solvent, as determined by the nature of the organic starting material. If the reaction has taken place in a closed vessel, or if solvents have been used, the product is recovered either by precipitation or by evaporation of the excess liquid present.

A reflux procedure was used for the first time in 1899 by the Aktiengesellschaft für Anilinfabrikation Berlin to produce a black dye from dinitrophenol (26). Patents which involve the use of indophenols and indamines specify reflux processes almost exclusively. The advantages of this procedure are several: (1) the temperature can be held more nearly constant; (2) finer adjustments of the temperature can be made; (3) the concentration can be more easily and exactly maintained; (4) the resulting product is usually the soluble and easily handled leuco compound; and (5) the possibility of overheating is largely excluded. The complex polyhydroxy, aminohydroxy, polyamino, and azine bodies are usually treated in this fashion too. The chief disadvantage of the method is the great length of time required for the reaction to go to completion at the lower temperatures usually employed. The soluble leuco compounds so prepared are usually precipitated by bubbling air through their aqueous solutions.

The usual temperature for open-kettle polysulfide fusion is about 150–200°C. There are instances, however, in which lower temperatures are employed, as well as a few others in which higher temperatures are specified. The reflux procedures are conducted, of course, at lower temperatures—at about 120°C. for those which use water as a solvent and 80–90°C. for those which use alcohol. When it is desirable to use a reflux procedure, but when a higher temperature is imperative, glycerol, amyl alcohol, β-naphthol, and similar substances are employed as solvents. The use of an autoclave permits intensive sulfuration at relatively low temperatures.

Patents which specify the fusion of organic substances with sulfur alone are not nearly so numerous as those requiring the use of polysulfides. This method came into use in 1893 with the preparation of Vidal's black dye (9). Sulfur can be substituted in most instances for polysulfides, but in some instances such a substitution yields different products. For the most part nitro compounds are not treated in this fashion, since they have a strong tendency to explode upon being heated with sulfur. As in the case of the polysulfides open-pot, pressure, and reflux procedures may be used with sulfur. The usual temperature for the open-pot sulfur process is 200–250°C. The patents indicate that in nearly every instance sulfur fusion yields insoluble thio bodies, which can be rendered soluble in water by treatment with molten sodium sulfide or with solutions of sodium sulfide. Palmer, Lloyd, and their coworkers report that the passage of organic vapors into molten sulfur at 240–260°C. yields resinous sulfur dyes which are soluble in sodium sulfide solution, but that identical vapors passed into molten

sulfur at 260–300°C. yield sulfur compounds which are not dyes and which are soluble in neither sodium sulfide nor carbon disulfide (70). By sulfur fusion a number of blue and black dyes are prepared from various amines, diamines, and phenols (27); the method finds its greatest use, however, in the fabrication of the yellow and brown dyes of the thiazole type (28). These latter are prepared, for the most part, in the presence of benzidine, whose participation in the reaction affects the color of the product considerably.

Sulfur monochloride is the third most common sulfurating agent, but even so, the patents citing its use are few. It is either refluxed with the organic material or is merely heated with it, usually in a closed vessel. The common temperature range for processes involving its use is 140–170°C., although the extreme limits are 80–200°C. The higher temperatures insure the reduction of the chloride to a complex mixture of sulfites, polysulfides, and thiosulfates which is apparently the real sulfurating agent. Treatment of the organic starting materials with sulfur monochloride generally yields either insoluble thio bodies, which are rendered soluble by treatment with sodium sulfide or sodium hydroxide, or sulfurated intermediate products which on fusion with sodium sulfide yield the dyes. A solvent may be used, but it must be inactive to both the organic material and the chloride. Carbon tetrachloride is most often used for the purpose, since it fulfills both requirements. The first patent involving the use of the monochloride as a sulfurating agent for the preparation of sulfur dyes was that issued to Cassella in 1897 for the fabrication of a black dye from *p*-aminophenol (29). With the exception of a few violet and reddish colors, all of those made in this manner are black or blue.

There are five other sulfurating agents which find a slight application in the production of the sulfur dyes. Of these five the thiosulfates of the alkali metals should be mentioned first. Upon being heated they decompose in a number of different ways, depending upon the temperature and other conditions, each of which yields one or more sulfurating media. The alkali metal salts of thiocarbonic and orthothiocarbonic acids, made by heating alcoholic carbon disulfide with sodium sulfide and sodium disulfide (Na_2S_2), respectively, are used in a few instances (30). A mixture of sulfur and fuming sulfuric acid which contains some sulfur sesquioxide (S_2O_3) will yield with certain organic compounds dyes which contain sulfur, but which because of their properties do not seem to be true sulfur dyes (31).

In some processes sodium sulfide alone is used to furnish the necessary sulfur. This compound may serve merely as a reducing agent as it does with 1,8- or 1,5-dinitronaphthalene (32), or it may cause dye formation by simultaneously serving as a reducing agent and as a sulfurating agent, as it does with the naphthalenesulfonic acids. The methods of applying sodium sulfide alone are, in general, identical with those for the application of the polysulfides.

A few black and blue dyes are prepared by passing hydrogen sulfide into solutions of the respective organic starting materials contained in a reflux apparatus. Modifications of the process require that an oxidizing agent be present and that the solution be acidic.

V. RESULTS OF VARIATIONS IN METHODS

Observations have been sufficiently extensive to lead to the generalization that in a majority of instances an increase in the temperature at which the sulfuration process takes place does not change the color of the resulting dye, but does deepen the shade of that color. Within limits the alteration of the shade will depend upon the extent of the temperature increase, and is generally regarded as being due to more intensive sulfuration at the advanced temperature (66, 72). A very few easily sulfurated starting materials yield dyes which show no change of shade as more heat is applied.

More intensive sulfuration than is usually to be obtained by an increase of temperature alone frequently produces increasingly deeper colors which may ultimately become black. This change is believed to be due to the formation of a greater number of sulfur-bearing ring structures in the fundamental structural units. Such extensive sulfuration is obtained by increasing the time of heating, by using increased pressures, by employing high-speed stirring, by using greater relative quantities of sulfur or the higher polysulfides, and by employing higher boiling liquids in reflux processes. These various methods may be applied singly or, as is often the case, combinations of them may be used. The choice of one or more of them is often determined by the nature of the starting material and by the result desired. When polysulfides are used as the sulfurating medium, the extent of the sulfuration depends upon the composition of the one chosen, provided all other factors remain constant. For example, m-dinitrotoluene yields with a polysulfide of the composition $Na_2S_2-Na_2S_3$ a water-soluble red-brown dye, while with $Na_2S_4 + S$ it yields an insoluble deep brown dye (1). Again, starting materials which are easily and more or less completely sulfurated by low polysulfides show little response to treatment with the higher members of the family.

Some organic starting materials yield different dyes with different types of sulfurating agents, while others show no differences. Because of the wide variety of behavior exhibited it is virtually impossible to frame a general statement which will cover all cases. Even among the compounds which show variations when treated with different agents, there seems to be no constant relationship between the properties of the dyes produced and the thionating agents employed. A number of organic substances which are sensitive to alkalies are sulfurated by sulfur melts. A number of other dyes which may be prepared by the use either of sulfur or of polysulfides seem to be identical, save that those prepared from the former are insoluble in water while those from the latter are water-soluble. Sulfur monochloride and trithiocarbonic acid yield dyes which generally are different from those prepared by the action of polysulfides upon identical starting materials.

The foregoing is practically all that can be said in a general way of the changes wrought in the sulfur dyes by variation of the method of thionation; however, it will be well to mention at this juncture several non-sulfurous substances which the patents show are used frequently in the preparation of these dyes and which may influence the color they impart to the fiber. If alcohol be employed as a

solvent in processes which take place at normal pressure, it seems to have no effect upon the product; however, when it is used under pressure, ethylation of the organic material present may occasionally result. The use of benzidine in sulfur fusions has already been referred to. Powdered copper metal and copper salts are frequently added to the dye melts. This treatment usually turns greenish shades to black, reddish ones to brown or violet, and yellowish ones to dull red, but there are recorded instances of its modifying the constitution of certain dyes without affecting the colors which they impart to the fiber (77). Fierz-David and his coworkers have established that the copper atom becomes an integral part of the dye molecule in the case of Pyrogen Green (SCI);[2] presumably this is true of other dyes fabricated in the presence of copper or copper salts, since the copper can be removed only after disintegration of the molecule has taken place (55). The salts of zinc, iron, chromium, and manganese are used similarly in a few processes, and a patent assigned to the General Aniline Works states that compounds of molybdenum, tungsten, vanadium, uranium, and antimony when added to the polysulfide melt of compounds of the type of 2-methyl-3-amino-7-hydroxy-5-ethylphenazine yield dyes of great color intensity (80).

Because of the present-day production of starting materials of a much more uniform quality and the availability of improved machinery and instruments for large-scale manufacturing, the sulfur dyes produced now are of a much more uniform shade than were those of the past. Careful adherence to empirical procedures based upon practical experience is also a factor in the preparation of more uniform products.

VI. GENERAL PROPERTIES OF THE SULFUR DYES

Although the numerous sulfur dyes are prepared from a great many different organic substances by sundry variations of a few general methods of sulfuration, their properties are very similar, varying in degree rather than in kind.

In general these dyestuffs are dark amorphous powders, many of which possess an almost metallic glint. Most of them are insoluble in water and in ether, acetone, the alcohols, aliphatic and aromatic hydrocarbons, dilute mineral acids, concentrated hydrochloric and acetic acids, and the mono- and poly-haloalkanes. Many of these dyes, however, are soluble in concentrated sulfuric acid, aqueous sodium sulfide, aqueous caustics, hot pyridine, and hot aniline (53). Examination of solutions of certain of the dyes with the ultramicroscope has shown them to be colloidal in nature, and x-ray diffraction photographs of a number of the dyes have been of the type characteristic of non-crystalline substances (41, 54). In the patents the chief properties listed are the colors the dyes exhibit in various solvents, but this is of small value since two or more dyes frequently produce similar colors. Occasionally the characteristic colors imparted to solutions in concentrated sulfuric acid are useful in demonstrating the existence of two differ-

[2] The letters appearing in parentheses after the trade names of dyes indicate their manufacture: e.g., (SCI) and (SCI in B) refer to the Society of Chemical Industry in Basle, (IG) refers to the German dye trust, and (C) refers to Cassella and Company in Frankfurt a.M.

ent dyes prepared from the same organic compound. The high-boiling organic compounds in which many of them are soluble rarely serve as media for the separation of mixture components. In alcohol those dyes which have been precipitated with acid are invariably insoluble, although the sodium salts of the same dyes are occasionally slightly soluble in it. In the latter case there is some question as to the identity of the soluble material, the suggestion having been made that it may be the sodium salt of an intermediate product (60). In pyridine there seems to be a reaction between the dye molecule and the solvent, and in boiling nitrobenzene the dye molecules undergo decomposition (41).

The insolubility of the dyes in water is, in a measure, dependent upon their method of preparation. All methods which do not employ alkalies or alkali salts produce dyes which are immediately insoluble. Those which result from dry fusion with alkaline substances or from refluxing with alkaline substances, such as alkali mercaptans, are immediately soluble, and the others can be rendered water-soluble by evaporation with alkaline solutions, or even by shaking with solutions of sodium sulfide or sodium hydroxide. These solutions are apparently colloidal, and the dye may be reprecipitated by neutralization with acid save in two recorded instances, or by bubbling air through the solution for a number of hours. The two dyes (33) which are not reprecipitated by acids are shown to possess unchanged amino groups and hence to be not entirely sulfurated. It should be noted that these two dyes which are soluble in dilute mineral acid also serve to dye wool as well as cotton. The materials which remain after treatments calculated to purify the dyes are much less soluble than the untreated dyes. This is presumed to be due to changes in constitution brought about by the treatment. Fierz-David suggests that in certain instances the treatment may possibly have the secondary effect of removing peptizing substances (41). The alkaline earth and heavy metal salts of the dyes are insoluble.

Rarely can a sulfur dye be purified sufficiently for much to be determined concerning its physical constants. Furthermore, the majority of the dyes undergo decomposition below their melting points. Even after preliminary washing to remove excess alkali salts, and further extraction with carbon disulfide to remove excess mechanically held sulfur, there still remains some unreacted sulfur. Frequently there are also present a number of high-molecular-weight compounds of different compositions.

Because of the difficulty of obtaining the dyes in a high state of purity, little can be said of their chemical properties save in a general way. Upon reduction with an aqueous solution of sodium hydrosulfite and sodium hydroxide the majority of the dyes yield soluble leuco compounds of a pale straw color. These, too, may be generally precipitated with dilute mineral acid, but the precipitates are even more quickly reoxidized than is the material held in solution. The sulfur dyes are preëminently dyes for cotton and as such are often applied as vat dyes from their leuco solutions, with the color being developed on the fiber either by air oxidation or by treatment with some one of the well-known oxidizing

agents. The other common method of application is to the unmordanted fiber from the colloidal solution of the dye in sodium sulfide.

The properties of many of the dyes are not altered even by reduction with zinc dust and acid, which causes the evolution of hydrogen sulfide (34). Grape sugar with strong sodium hydroxide solution and certain other strong reducing agents act upon nitrogen-bearing dyes to bring about the evolution of ammonia and a condensation which effects a complete change of properties (61). Reduction with stannous chloride and strong acid of dyes prepared from diphenylamine derivatives brings about the evolution as hydrogen sulfide of a portion of the sulfur contained, with accompanying degradation of the dyestuff (54).

The leuco form of the dyes is readily oxidized, and the dyes themselves undergo oxidation when heated alone or with various strong oxidizing agents. Sodium peroxide fusion converts the sulfur to sodium sulfate, and hot concentrated sulfuric and nitric acid each forms some sulfates also. Upon treatment with the last-named agent, dyes prepared from diphenylamine derivatives yield also a product which has a strong odor of nitrobenzene (53).

So far as is known, only one of the dyes has ever yielded a crystalline bisulfite complex upon treatment with sodium bisulfite. This single success was achieved by Gnehm and his coworkers with Immedial Reinblau (47). By sulfite or bisulfite treatment other dyes are usually converted to water-soluble sulfonic, sulfinic, or thiosulfonic acid derivatives (35).

The majority of reagents either do not attack the dyes at all or else decompose them completely.

One of the most serious disadvantages of the sulfur colors is the extreme sensitivity of a majority of them to chlorine—a sensitivity which is retained after their deposition on the fiber.

It is reported that alkyl substitution of either the dyes or their leuco bases, either on or off the fiber (36), occurs readily provided only that the compound to be alkylated is of a mercaptan nature (37).

Other reported properties are of insufficient generality to warrant mention here.

VII. CONSTITUTION OF THE SULFUR DYES

The discovery of the sulfur dyes, besides instigating much commercial research on intermediates and methods of preparation, also inspired a considerable amount of purely scientific research which had for its aim the determination of their chemical nature and constitution. Work of this kind was begun shortly after the discovery of Croissant and Bretonnière was made public. Given added impetus by Vidal's discoveries and studies on the constitution of his black dye, it was continued by sundry investigators in various laboratories in England and on the Continent until about 1910, when it practically stopped, slowed by the burden of its own discouraging results. During the first half of the last decade there was again a flurry of interest in the constitution of these dyes, but at present activity in the field has again almost reached the vanishing point.

Because of their insolubility, the variability of their composition, and the difficulty encountered in purifying them, their unresponsiveness to any save the most drastic treatments, and the complexity of their structures, the sulfur colors have withstood the majority of attempts to fathom the mystery of their constitutions. As a result of the work that has been done, a number of well-founded theories have been proposed, but the exact constitution of no single dye is authoritatively known. For a time it was thought that the constitution of one dye, Immedial Pure Blue (13), had been established, but there is reason to believe that the proposed structure is that of a fragment rather than of the dye molecule as a whole (41). A study of the assembled data shows that the general nature of the dyestuffs is fairly well agreed upon; the blacks, blues, and some of the greens and Bordeaux-reds are generally held to be thiazine derivatives, while the majority of the yellows and browns are apparently thiazole derivatives. Thianthrene, acrithiole, piazthiole, and other fundamental ring structures have been proposed for various individual dyes, but subsequent investigations do not indicate that such structures are common among the sulfur colors. Investigations into the manner in which sulfur contained in side chains is held have also been interesting.

The sensitivity of the sulfur dyes to heat, the fact that they cannot be obtained in a crystalline form, and their tendency to form colloidal solutions have made molecular-weight determinations impossible, thus blocking the establishment of molecular formulas and largely limiting the work of investigators to the proposal of structural units of the large molecules. All indications are that their molecular weights are large.

A. *Sulfur in the fundamental ring structures*

That many of the black, blue, and green sulfur dyes contain the thiazine ring system as the fundamental building unit of their molecules has been established by the collection of a plethora of data. The preparation of sulfur dyes from methylene blue, whose thiazine nature was known, and from certain thiosulfonic acids of benzene derivatives gave an early indication of the thiazine nature of these dyes. Furthermore, certain indophenols and indamines which are starting materials for the sulfur dyes will yield, upon being converted into thiosulfonic acids and treated with dichromate, black and blue dyes which can be distinguished from the sulfur dyes only by a study of their characteristics of fastness (48). These dyes are shown to be derivatives of thiodiphenylamine. Bernthsen (3) has further substantiated this view by the preparation of sulfur dyes from methylene violet and from the product obtained by treating the mercaptan of the condensation product of dihalohydroquinone and dimethyl-*p*-phenylenediaminethiosulfonic acid. This seems to prove beyond a doubt the thiazine natures of these several dyes, for the stability of the thiazine ring in polysulfide melts follows from the formation of similar sulfur dyes by the treatment of methylene violet with sulfur, trithiocarbonic acid, sulfur monochloride, etc.(62).

Vidal's earlier researches also point to the existence of thiazine rings in the sulfur blues and blacks (81). He found that heating ammonia, sulfur, and quinone together produced leucothionol,
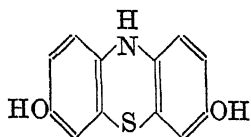
which is also produced along with a black dye when sulfur and *p*-aminophenol are heated together, and again when molecular portions of *p*-aminophenol, quinol, and sulfur are heated together. He also found that by heating together quinol, *p*-phenylenediamine, and sulfur he first obtained leucothionoline,
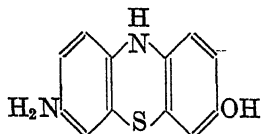
and subsequently, upon further heating of the mixture with sulfur, a black dye. His work, while lacking much in completely elucidating the structure of the dyes which he studied, does offer further evidence for the thiazine nature of such dyes. The Clayton and dinitrophenol blacks (*cf.* Immedial Black) are distinguished from Vidal Black by a considerable difference in properties, but they too have been shown to have the thiazine ring as their fundamental structure (63).

In their investigation of blue, green, and Bordeaux-red sulfur dyes prepared by refluxing some of the simpler derivatives of diphenylamine with polysulfides in an aqueous medium, Jones and Reid (54) found evidence which indicated that the thiazine ring was the fundamental unit of structure in each case. The two Bordeaux-red dyes prepared from *p*-hydroxydiphenylamine and *p*-methyl-*p'*-hydroxydiphenylamine were shown to be very similar in properties to Bernthsen's (4) oxothiodiphenylimide, which is also of a reddish color, and whose formula has been established as
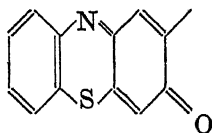
Still more recent work performed by Fierz-David and his coworkers (2, 41, 42, 55) on a variety of blue, green, and black sulfur dyes indicates that here again the thiazine ring is the fundamental structure. The work of these investigators upon Pyrogen Indigo (SCI in B), Hydron Blue (IG), and certain of the other blue dyes is reported as confirmed by Hatirō Hiyama (49).

The formation of thiopyrone rings
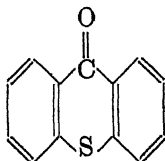
is generally believed to occur in the formation of a few sulfur dyes, notably those prepared from fluorescein by Wichelhaus, Vieweg, and others (38), though

incontrovertible proof remains to be established. There is also a very good likelihood that the dyes prepared from diphenylamine disulfide contain the thianthrene ring, but such dyes are in the minority.

At various times in the past piazthiole, hypothetical acrithiole, and oxazine structures have been proposed as possible components of sulfur dyes, but to date both investigational data and theoretical considerations give no support to the idea.

Thus far the preponderance of evidence indicates that the thiazine ring is the fundamental ring system of black, blue, green, and Bordeaux-red sulfur dyes—especially when derivatives of diphenylamine have been the starting material.

The yellow and brown sulfur dyes, produced largely from toluylene-2,4-diamine, tolidine, and similar compounds containing carbon in the side chain, have been found to resemble dehydrothiotoluidine and primuline in that they contain the thiazole group,
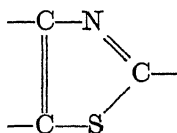
which has been shown to be the fundamental structure of these dyes, although the complete unit structures have been worked out only in a few cases. The initial investigation of dehydrothiotoluidine was begun by Jacobsen (51) and continued by him and others until the constitution of this substance was finally established by Pfitzinger and Gatterman (71) as being that of p-aminobenzenyl-aminothiocresol:
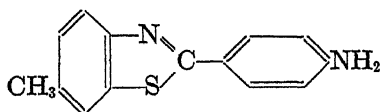
In the yellow and brown sulfur dyes the sulfur of the thiazole ring is introduced by the direct interaction of sulfur and the organic starting material. As a result of this treatment there is obtained a colored, insoluble mass which can be rendered soluble by treatment with a hot, concentrated, aqueous solution of sodium sulfide. This treatment introduces mercaptan groups into the molecule, making it that of a true sulfur dye. The work of Fierz-David and his coworkers (41, 42) also supports the thiazole nature of certain of the yellow, orange, and brown dyes.

It is assumed, though there is no conclusive proof, that the yellow and brown dyes prepared in the presence of benzidine may contain the dibenzothiophene ring system,
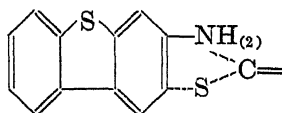
either alone or in union with the thiazole ring as indicated.

The proposal of Ris that in certain instances a hypothetical ring isomeric with thiazole, which structure he called acrithiole, might be present has never received any support; on the contrary, in fact, it was largely discredited by the work of Biedermann (5).

At the present time the thiazole nature of the majority of such dyes seems well established.

B. Sulfur in the side chains

Thus far in this discussion of constitution mention has been made only of the sulfur contained in the fundamental ring structures. Sulfur so held is perhaps in the most fundamental union, but usually it represents only a small portion of the total sulfur content of the dye. Dyes prepared both commercially and in the laboratory have been shown to contain both mechanically held sulfur and sulfur-bearing impurities, but even when these have been removed by extraction with dilute acid and base, ether, alcohol, carbon disulfide, etc. (41, 54), the sulfur content of many dye molecules remains relatively high (frequently 30–35 per cent). In the different sulfur colors varying numbers of sulfur-containing side chains are known to be present; although few constitutions are definitely known, of the existence of such side chains there can be no doubt. The work of many investigators substantiates their existence.

A majority of the sulfur-bearing side chains introduced into the dye molecule by polysulfide fusion are held to be the sodium salts of mercaptan groups, ZSNa, which are responsible for the solubility of most dyes prepared by this method. The insoluble, fast, oxidized form of the dye which appears on the dyed fiber is held by this school to be the disulfide, Z—S—S—Z (45). It is further maintained that the mercaptan and disulfide groups, aside from influencing the solubility of the dye, have nothing to do with their ability to dye unmordanted cotton fiber. It was the view of Vidal that the solubility of these dyes was due largely to their phenolic natures (82). The fact that the dyes can be alkylated to form thioethers is irrefutable proof of their mercaptan nature (64). Furthermore, it is well known that even after the dyes have been set to the fiber they may still be alkylated. This would indicate either that if they exist on the fiber as disulfides they still contain unchanged mercaptan groups, or that the mercaptans which were oxidized to disulfides may be reformed by the alkylating agents and then alkylated to produce the color changes usually noted during the process. This latter possibility seems the more likely.

The mercaptan groups, though exerting a great influence on the solubility of the dyes, seem to exert none on their origin and fundamental structure, for frequently by the introduction of a mercaptan group, or of several such groups, into dyestuffs of other classes there will result sulfur dyes which will still retain the tinctorial properties of the class of which they were originally members.

The position of the mercaptan groups in the dye is of considerable importance. A single sulfhydryl group generally enters the position ortho to an amino or hydroxyl group (i.e., to an auxochrome group) of the mother substance (46). The ease with which halogen substituents may be replaced by mercaptan groups

has been of great value in making these determinations of position. The position of mercaptan groups in dyes prepared from halogen-containing indophenols can be established thus with great certainty, for by polysulfide fusion as many sulfhydryl groups as there are halogen groups can be introduced into the indophenol, its leuco base, or its corresponding dinitrodiphenylamine derivative. It must be pointed out, however, that ordinary fusion apparently does not eliminate halogens in the phenylated side chains of an indo body (65).

Not all of the properties of the sulfur colors are explained by the foregoing proved structures. For instance, the production of dyes of several different shades from the same mother substance by variation of the conditions of sulfuration cannot be explained on the basis of a common structure, and variation of the number of mercaptan groups upon a common fundamental ring system has been shown to have no effect upon the color. Such considerations led Möhlaus to propose polysulfide chains rather than the mono- or di-sulfide linkages. He and Seyde (68) began their work on the sulfuration of phenol, a reaction which they represented thus:
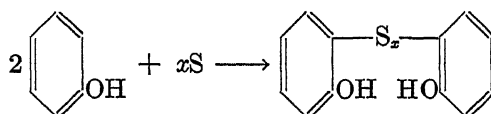
From the reaction product they were able to isolate the disulfide, which was poorer in sulfur than the rest of the product from which it was removed. They concluded from their work that the connecting sulfur chain can be as long as eight atoms (67). The work of Jones and Reid further substantiates the existence of polysulfide chains in the dyestuffs of a thiazine nature (54). These investigators were able to show that the compounds

and
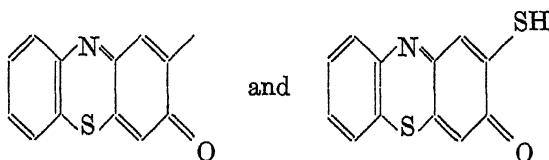
do not yield hydrogen sulfide when treated with stannous chloride and strong acid, but that the sulfur dyes of a thiazine nature do lose as hydrogen sulfide all of their sulfur atoms in excess of those in the thiazine structure and those which are attached directly to the ring. The existence of polysulfide chains seems highly likely from a theoretical consideration, for without them a number of characteristic properties are explained only with difficulty. The existence of such polysulfide bridges helps to explain the existence of the ultra-large molecules, or colloidal aggregates, which are known to exist.

Möhlaus assumes also that in the thiazole, thiazine, and azine structures there may be polysulfides where it is usually the custom to write only a single sulfur atom. The strongest support for this idea is offered by his work of increasing the sulfur chain of Immedial Black to produce a dye of the same color but of different properties. The work of Schultz and Beyschlag (73) substantiates the

polysulfide theory of Möhlaus, and it is their conclusion that the sulfuration of organic substances for the production of sulfur dyes leads to no definite products.

No mention is made here of Erdmann's (40) thiozonide theory, because so little importance attaches to it at the present time.

Further light has been thrown upon the mechanism of the sulfuration process from the standpoint of the sulfur compounds involved, by the work of Khmelnitzkaya and Verkhovskaya (56), who report that in the formation of the black dye from sodium dinitrophenolate and sodium pentasulfide (Na$_2$S$_5$) in water, sulfuration and reduction proceed simultaneously. They represent the reduction thus:

$$R(NO_2)_2 + 2Na_2S_x + 2H_2O \rightarrow R(NH_2)_2 + 2Na_2S_2O_3 + S_{x-2}$$
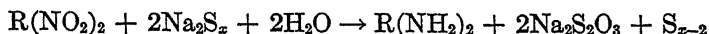
and state that the sulfur set free is in an active form which sulfurizes the amine to produce the dye. Such a mechanism is proposed for the dyes prepared from polysulfides and the various types of organic amines as well as for the Immedial indone dyes. The work of Richard Herz has also been of importance in throwing light upon the possible reactions involved in sulfuration (83).

C. Proposed constitutions of the units making up sulfur dye molecules

The fact that the majority of sulfur dyes cannot be obtained in crystalline form and that in most cases they form colloidal solutions has not only made studies upon constitution difficult, but has also prevented investigators from doing more than proposing the formulas of the units of which the macromolecules are composed. Despite the quantity and excellence of the work upon which these proposals are based, their correctness may still be questioned because of the treatments required to purify the dyes and to convert them into derivatives. Among the most recent suggestions are those of Fierz-David and his coworkers (41) and of Jones and Reid (54).

For the units of which the Immedial Pure Blue (C) molecule is composed, Keller (55) and Fierz-David propose the formula
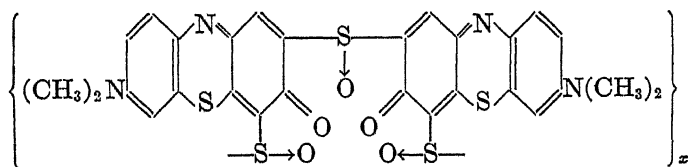
For the other blue, green, and black dyes which they investigated the Fierz-David workers propose similar unit formulas in which two substituted thiazine ring systems are bound together by an SO bridge, save in the case of Pyrogen Green (SCI in B). In this latter case both SO and disulfide links were proposed. This group of workers used both commercially prepared dyes and dyes made by the method of Herz (83) from the same intermediates used for their commercial counterparts. The pairs of dyes made from the same intermediates were not identical in properties nor did they have identical sulfur and oxygen contents.

In the case of each dye for which a formula was proposed, the number of thiazine rings in the fundamental structural unit was determined by the titanous chloride titration method of Knecht and Hibbert, but for this titration the dyes had to be rendered soluble by sulfonation. This chemical treatment and the recorded results of the titrations themselves (save in the case of Pyrogen indigo) leave room for question. The presence of the thiazine structure in each case was confirmed, however, by spectroscopic investigation, and the treatment of the leuco compound of Pyrogen indigo with chloroacetic acid produced a derivative which apparently confirmed the existence of two thiazine rings per unit for that dye. The presence in the dyes of groups (presumably disulfides) which upon reduction yield mercaptans is adequately demonstrated.

Continued strong sulfuration of a Bordeaux-red dye prepared by Fierz-David and Zürcher (41) from *p*-anisidine yields a product which becomes darker and darker and finally black, and whose methoxyl content becomes at the same time progressively smaller. It is the assumption of these investigators that further thionation is able to take place at a free para position, or at an occupied para position after elimination of the substituent already there, with the formation of a larger number of thiazine groups, or of other sulfur-bearing groups such as the thioxonium ring. Such drastic treatment apparently introduces also some sulfonic acid groups which, coupled with the mixtures which naturally result from such treatment, make these sulfur blacks of high sulfur content very difficult to purify and to work with in general.

The work of Jones and Reid (54) also indicates the presence of the thiazine ring structure in the blue, green, and Bordeaux-red dyes which they investigated. While not conclusive, their work also indicates the presence of polysulfide side chains of the variety proposed by Möhlaus. There is little evidence of the number of oxygens found by Fierz-David and his coworkers. These investigators, who prepared all of their dyes by treatment of diphenylamine derivatives with aqueous sodium polysulfide, suggest units linked by polysulfide chains as composing the macromolecules. Some of the suggested units are: for the dye from *p*-hydroxydiphenylamine
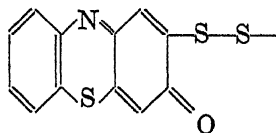
for the dye from *p*-methyl-*p'*-hydroxydiphenylamine
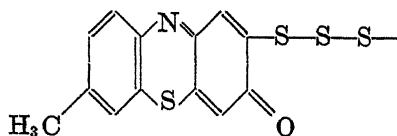
and for the two green dyes prepared from *p*-amino-*p'*-hydroxydiphenylamine

and
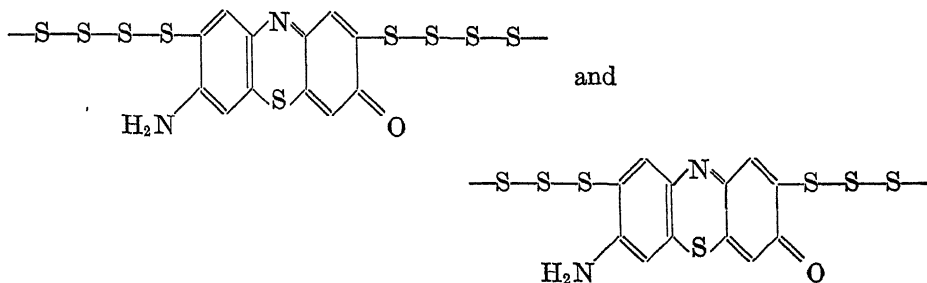
VIII. CONCLUSION

From the foregoing discussion it is apparent that the sulfuration of organic compounds to produce sulfur dyes proceeds by a few well-defined processes which involve the use of only a limited number of sulfurating agents and which may be so controlled as to produce compounds of given tinctorial properties. Since the first investigation of structure undertaken by Vidal in 1893, many investigators have sought to determine the constitution of a variety of these dyes. As a result of this work the general nature of the dyes is known, but because of the general insolubility of the dyes and their resistance to all save the most drastic treatment, little is known with certitude of the constitutions of the individual dyes. Constitutions of the units of which the macromolecules of a number of the individual dyes are composed have been suggested by several investigators, but though these rest upon good evidence, even they are open to some question.

The researches of the past have been valuable and they have in many instances been ingenious, but perhaps their chief value has been to point the way to further investigations in a field where much remains to be learned and where laborers have been all too few. Investigations conducted with the aid of the new tools of modern physics might succeed in bringing order to the knowledge of this division of tinctorial chemistry.

IX. REFERENCES

 (1) Anmeldung K. 23049, Kalle and Company (1902).
 (2) BERNASCONI AND FIERZ-DAVID: Helv. Chim. Acta 15, 287 (1932).
 (3) BERNTHSEN: Ann. 251, 97 (1889).
 (4) BERNTHSEN: Ann. 230, 182 (1885); Ber. 17, 2860 (1884).
 (5) BIEDERMANN: Ber. 10, 1161 (1877); cf. also D.R.P. 126,964 and 128,659.
 (6) CLEMM: J. prakt. Chem. 109, 178 (1870).
 (7) D.R.P.[3] 84,632 (1893); 91,719 (1894).
 (8) D.R.P. 85,330 (1893).
 (9) D.R.P. 82,748 (1894).
(10) D.R.P. 103,861 (1897).
(11) D.R.P. 103,646 (1897).
(12) D.R.P. 106,030 (1898).
(13) D.R.P. 134,947 (1900).

 [3] German patent.

(14) D.R.P. 152,373 (1903); 161,462 (1903); 177,709 (1905); 181,125 (1905).
(15) D.R.P. 126,175 (1900).
(16) D.R.P. 101,577 (1896).
(17) D.R.P. 135,410 (1901).
(18) D.R.P. 126,964 (1900); 128,659 (1901).
(19) D.R.P. 139,430 (1902); 144,762 (1902); 152,595 (1902).
(20) D.R.P. 218,371 (1908); 221,215 (1909); 222,640 (1909); 238,857 (1910).
(21) D.R.P. 91,508; 95,484; 204,772.
(22) D.R.P. 185,663.
(23) D.R P. 162,156; 187,823; et al.
(24) D.R.P. 129,325.
(25) D.R.P. 132,221.
(26) D.R.P. 127,835 (1899).
(27) D.R.P. 167,769; 149,637; 117,921; 131,999.
(28) D.R.P. 146,917; 152,595; 154,108; et al.
(29) D.R.P. 103,646.
(30) D.R.P. 138,255; 141,461.
(31) D.R.P. 205,216; 242,215.
(32) D.R.P. 84,989.
(33) D.R.P. 99,039; 114,802.
(34) D.R.P. 125,857; 126,964; et al.
(35) D.R.P. 88,392; 91,720; et al.
(36) D.R.P. 134,962; 134,176; 131,758.
(37) D.R.P. 131,758.
(38) D.R.P. 52,139; 114,268; 220,628; Ber. **33**, 2570 (1900); **32,** 1127 (1899).
(39) E.P.[4] 1489 (1873).
(40) ERDMANN: Ann. **362**, 133 (1908).
(41) FIERZ-DAVID: J. Soc. Dyers Colourists **51,** 50–63 (1935).
(42) FIERZ-DAVID: Naturwissenschaften **20**, 945-7 (1932); Chem. Abstracts **27**, 1513 (1933).
(43) FRIEDLAENDER: Fortschritte der Teerfarben-Industrie, volumes at intervals since 1899. J. Springer, Berlin.
(44) Reference 43, Vol. VI, p. 611.
(45) FRIEDLAENDER: Z. angew. Chem. **19**, 616 (1906).
(46) FRIEDLÀENDER: Z. angew. Chem. **19**, 615 (1906).
(47) GNEHM AND COWORKERS: J. prakt. Chem. [2] **69**, 169 (1904); Ber. **37**, 2618 (1904).
(48) GREEN AND PERKINS: J. Chem. Soc. **83**, 1201 ff. (1903).
(49) HATIRŌ HIYAMA: Kwagaku to Kōgyō (Science and Ind.) **16**, 230-5 (1941); Chem. Abstracts **36**, 1181 (1941).
(50) HAYNN: Textile Colorist **58**, 257-8 (1936).
(51) JACOBSEN: Ber. **22**, 330 (1889).
(52) JONES: J. Chem. Soc. **37**, 461 (1880).
(53) JONES, W. N., JR.: Doctoral Dissertation, The Johns Hopkins University, 1932.
(54) JONES AND REID: J. Am. Chem. Soc. **54**, 4393 et seq. (1932); Chem. Abstracts **27,** 94 (1933).
(55) KELLER AND FIERZ-DAVID: Helv. Chim. Acta **16**, 585 (1933).
(56) KHMELNITZKAYA AND VERKHOVSKAYA: Anilinokrasochnaya Prom. **2**, No. 1, 31-4 (1932); Chem. Abstracts **26**, 4590 (1932).
(57) LANGE: Die Schwefelfarbstoffe, ihre Herstellung und Verwendung, 2nd edition, p. 5. Spamer, Leipzig (1921).
(58) Reference 57, p. 262.
(59) Reference 57, p. 135.

⁴ British patent.

(60) Reference 57, p. 15.

(61) Reference 57, p. 16.

(62) Reference 57, p. 35.

(63) Reference 57, p. 51.

(64) Reference 57, p. 65.

(65) Reference 57, p. 74.

(66) Möhlaus: *Eigenbericht auf der Versammlung deutscher Naturforschung und Ärtze,* Dresden (September, 1907); Chem.-Ztg. **31**, 937 (1907).

(67) Möhlaus: Z. physik. Chem. **54**, 274 (1906).

(68) Möhlaus and Seyde: Chem.-Ztg. **31**, 937 (1907).

(69) Palmer and Lloyd: J. Am. Chem. Soc. **52**, 3388–95 (1930); *cf.* reference 70.

(70) Palmer, Lloyd, *et al.*: J. Am. Chem. Soc. **62**, 1005–6 (1940); U. S. patent 1,884,762 (October, 1932).

(71) Pfitzinger and Gatterman: Ber. **22**, 1063 (1889).

(72) Schultz and Beyschlag: Ber. **42**, 743, 753 (1909).

(73) Schultz and Beyschlag: Ber. **42**, 743, 753 (1909); Chem.-Ztg. **31**, 937 (1907).

(74) Schwalbe: Z. angew. Chem. **20**, 433 (1907).

(75) Thorpe: *A Dictionary of Applied Chemistry,* revised edition, Vol. VI, p. 495. Longmans, Green and Company, London (1926).

(76) Reference 75, p. 495.

(77) Reference 75, p. 507.

(78) Troost: Jahresber. Chem., p. 958 (1861).

(79) U. S. patent 1,098,259.

(80) U. S. patent 1,886,365 (1932).

(81) Vidal: Mon. sci. **11**, II, 655 (1897); **17**, 427 (1903); D.R.P. 99,039.

(82) Vidal: Mon. sci. **19**, 25 (1905); Chem. Zentr. **1905**, I, 411.

(83) von Weinberg: Ber. **63**, 117 (1930).

(84) Witt: Ber. **7**, 1530, 1746 (1874).

BIOLOGICAL METHYLATION

FREDERICK CHALLENGER

Department of Organic Chemistry, The University, Leeds, England

CONTENTS

I. INTRODUCTION

As long ago as 1815, more or less severe cases of arsenical poisoning occurred in Germany and were ascribed to the use of domestic wall-papers the pigments on which were shown to contain arsenic. At that time the use of copper hydrogen arsenite and similar colors (Scheele's green and Schweinfürter green) for the decoration of houses was common. Since then, in spite of rigorous legislation, several similar cases—some fatal—have occurred from time to time.

Summaries of the earlier literature on this subject (with extensive bibliographies containing numerous references to its medical aspects) have been published by Abel and Buttenberg (4), Huss (136), and Maassen (152). The next few pages of this review contain a chronological account of the development of ideas concerning the origin of these toxic effects and the nature of the arsenical compounds producing them. It may be stated at once that the toxic compound has been shown to be trimethylarsine and that moulds growing on the damp wall-paper are responsible for its production. This conclusion gave to the phenomenon a much wider significance, methylation being a well-recognized bi-

ological process which, in some instances, seems to be employed for detoxication purposes.

The earliest and most obvious explanation put forward to explain the absorption of arsenic by persons living in the rooms was the inhalation of particles detached from the paper. The presence of arsenic in the dust of such rooms had been demonstrated (for references see Abel and Buttenberg (4) and Huss (136)), but poisoning had also been observed where the original arsenical paper had been covered by a fresh one containing no arsenic (Fleck (86); see also Huss). Consequently it was necessary to look for some other cause than mechanical disintegration of the pigment. Gmelin (98) in 1839 noticed that a garlic odor was usually present in rooms where the symptoms had developed. He ascribed the poisoning to a volatile arsenic compound liberated from the wall-paper which, in his experience of such cases, was usually found to be damp and mouldy. Further indications in this direction were obtained in 1872 by Fleck (86), who exposed strips of paper coated with Schweinfürter green (copper arsenite containing copper acetate) to moist air in flasks. The strips were attached to the walls with starch paste and after a time became mouldy. Air was passed through the flasks and led into silver nitrate solution, giving a deposit which appeared to be silver. On removing this and adding ammonia, a precipitate of silver arsenite was thrown down. No chemical evidence for the identity of these deposits was given by Fleck.

Two years later, Selmi (189) suggested that the moulds on the wall-paper and in Fleck's experiments might play a definite part in the volatilization of the arsenic by producing hydrogen from the paper and paste which, acting on the arsenical pigment, gave rise to arsine. This hypothesis had at first sight much to recommend it. Hydrogen is now known to be produced from carbohydrate by many microörganisms, though not by moulds, but it would appear probable that Fleck's strips of paper ultimately harbored a very mixed microbiological flora.

A suggestion that the gas was arsine had already been made by Martin (153) in 1847 but without reference to mould action. Later, however, this view had to be abandoned. There is no evidence that arsine is concerned in the phenomenon in any way, but moulds have been shown to play an essential part in the process.

In their very useful summary Abel and Buttenberg refer to a case where an arsenical paint on a wall gave rise to no trouble until it was covered up with arsenic-free paper attached by means of some, presumably organic, adhesive. Vallance (203) quotes a case recorded by Scheringa (187) where an arsenical odor was reported in a room. The outer wall-paper gave a negative test for arsenic, but older paper underneath gave a strong positive test, the arsenic being almost completely soluble in water. It was discovered, however, that fifteen years previously the paperhanger had mixed rat poison with the paste to prevent mice from gnawing the paper. Re-papering from time to time had evidently furnished nutrient material for the fungi which converted the arsenic to volatile compounds.

In the light of more recent work it is interesting to recall that in 1846 Basedow

(15) suggested that the air of the "arsenical rooms" might contain cacodyl oxide, $(CH_3)_2AsOAs(CH_3)_2$, which was originally obtained by Cadet (48) in 1760 by heating a mixture of arsenious oxide and potassium acetate, and was exhaustively studied later on by Bunsen (40–46). Basedow (15) brought forward no evidence in support of his suggestion, which was doubtless made owing to the very great interest aroused by Bunsen's experiments at the time.

The work of Gosio and Biginelli

Up to 1891, therefore, very little reliable information existed as to the manner in which toxic products are evolved from arsenical wall-paper and opinions on their nature were based on little or no experimental evidence. In this year Gosio (101) began a systematic study of the whole question. He exposed a potato-mash containing arsenious oxide to the air and observed that it quickly became infected with various moulds and bacteria and evolved a garlic odor. He isolated some of these organisms in pure cultures and studied their effect on various media containing carbohydrate and arsenious oxide and also certain arsenical pigments. The bacteria produced no volatile odorous compound of arsenic under these conditions (see also page 327), but some of the moulds were intensely active in this respect, especially one which Gosio named *Penicillium brevicaule* and which Saccardo (184) had first isolated from decomposing paper. Gosio also isolated this mould from a carrot. Other organisms which exhibited this phenomenon were *Aspergillus glaucus*, *A. virens*, and *Mucor mucedo*. Thom and Raper (202) have recently extended this list to include *A. fischeri*, *A. sydowi*, and a few soil organisms.

With the aid of pure cultures of *Penicillium brevicaule*[1] Gosio elaborated a biological method (101, 102, 103) for the detection of minute traces of arsenic in materials of the most varied type. The substance to be tested was extracted with water or dilute acid, the solution evaporated, and small quantities of the residue added to a slice of sterile potato previously inoculated with the mould. On maintaining the culture at a temperature of about 25–30°C. the presence of any inorganic compound of arsenic could be detected after a few hours by the production of a more or less intense garlic odor. Smith and Cameron (194) have stated that as little as one-millionth of a gram of arsenious oxide in 1 g. of material can be recognized in this manner; the reaction is qualitatively much more delicate than the Marsh test but is not readily adaptable to quantitative purposes.

Gosio then turned to the chemical examination of the volatile arsenic compound to which the odor is due and which is often known as Gosio gas. He removed the gases from a large number of cultures of *S. brevicaulis* on potato-mash in a stream of air and passed them through a red-hot tube, weighing the carbon dioxide and water produced. He concluded that the gas contained an alkyl-arsine, probably diethylarsine, $(C_2H_5)_2AsH$, although at the time this substance had not been prepared.

[1] The modern nomenclature is *Scopulariopsis brevicaulis*, which will be used in future references to this organism.

Gosio's work was continued by his assistant Biginelli (24), who aspirated the gas evolved from cultures of *S. brevicaulis* on potato-mash containing arsenious oxide through mercuric chloride dissolved in dilute hydrochloric acid. The resulting precipitate was assigned the composition $(C_2H_5)_2AsH \cdot 2HgCl_2$. Biginelli, therefore, concluded that the gas was diethylarsine. Klason (143), however, from a reconsideration of Biginelli's analyses and some further work, regarded it as diethylarsine oxide. Wigren (216) synthesized both these compounds and showed that their behavior towards acid mercuric chloride (Biginelli's solution) was different from that of Gosio gas, a conclusion confirmed by the later experiments of Ellis (61) in Leeds.

Meanwhile Cevey (51) had made the important observation that a garlic odor is also evolved when the inorganic arsenic of the cultures is replaced by sodium cacodylate, $(CH_3)_2AsOONa$. This was confirmed by Pool (175) with the mould *Monilia sitophila* Saccardo.

The Forest of Dean case

While the identity of Gosio gas was still in doubt, the deaths of two children in the Forest of Dean were reported (71) in December, 1931. The parents and two other children were also affected. The following account of the proceedings at the inquest is taken from *The Analyst* (8): Professor H. A. Scholberg, of University College, Cardiff, said that he had made a microscopical and bacteriological examination of the lungs of the boy. He attributed the death to bronchial pneumonia and blood poisoning. The jury were of the opinion that there was not sufficient evidence to show that the arsenic found had contributed to the death.

At the inquest on the girl, Mr. R. H. Ellis, F.I.C., County Analyst, said that he found arsenic in certain organs of the body (*viz.*, intestines, liver, kidneys, and lungs), the total amount (as arsenious oxide) being 2.65 mg. He had also analyzed samples of the wall-paper and of the plaster. In the paper from a dry part of the wall he had found 8.3 parts per million of arsenious oxide; in samples from a part where the mould was most pronounced there were 2.3 parts per million; and in the plaster there were 91 parts. An unused roll of wall-paper, purchased at the same time, contained 4.4 parts of arsenic per million. He had found definite traces of arsenic being given off in gaseous form from the wall that was affected by mould, and it was significant that the arsenic content of the mouldy wall-paper was only half that in a portion of the new paper, and only a quarter of that in a sample of the same paper taken from a dry part of the wall. In his opinion, the arsenic in the paper was present as an impurity, and he attributed the trouble to the plaster, and not to the paper. The arsenic in the plaster, which was composed of coke-breeze and cement, would dissolve in the moisture coming through the wall from the bank of soil outside, and the mould would then grow on the paper and would liberate the arsenic in the form of a very deadly organic compound. Mr. Ellis added that other tests made by him showed that four of the six members of the family had traces of arsenic in their systems. The jury returned a verdict that death was due to dysentery and to exposure to arsenic, which was generated in the house in a gaseous form.

Note by the Editor of The Analyst:

Mr. Ellis has informed the Publication Committee that consideration was given to the possibility of the quantity of arsenic found being present without any question of poisoning, but the distribution of the quantities found was also taken into account and considered in connection with the pathological condition of the organs. One of the chief factors which led to the conclusion formed was the fact that the amount of arsenic found in the lungs was greater in parts per million than in any other part of the body, except the large intestine, and this agreed with the condition of the lungs.

The problem of proving the presence of arsenic in the air was more difficult, and an attempt to detect it by simple aspiration gave negative results. Experiments were, therefore, made by exposing filter papers, saturated with silver nitrate, on the walls of the house, and these were left for 7 and 9 days, respectively. When these filter papers were destroyed, in the usual way, and the amount of arsenic was determined by the electrolytic Marsh test, small mirrors of arsenic were obtained.

The desirability or otherwise of the use for building purposes of materials which contain arsenic and also the use of arsenical preservatives in building construction has been briefly discussed elsewhere by the author (52; see also references 21, 77, 144, 146, 207, 219). In a recent letter to the author Mr. R. H. Ellis (80) states that he has investigated two other cases of (non-fatal) poisoning in a room in an ecclesiastical building used as an office and has demonstrated the presence of a volatile compound of arsenic in the air of the room. The walls were damp and stained and "there was some evidence of the growth of moulds, though nothing like so much as was present in the Forest of Dean case." As Mr. Ellis may be publishing his results elsewhere, further details can be omitted.

Identification of Gosio gas

Owing to the uncertainty regarding the nature of Gosio gas, a study of the subject was commenced at the University of Leeds (61) in the late autumn of 1931. In May 1932 the gas was identified as trimethylarsine, $(CH_3)_3As$.

Four strains of *Scopulariopsis brevicaulis* (Thom) were employed. Bread crumbs (with or without added water) were used in conical flasks such that after sterilization (25–30 min. at 120°C. or 30 min. at 100°C. on three successive days) a layer 1–1.5 in. deep was obtained. For a 1-liter flask 150–200 g. of fresh crumbs was required. These were inoculated with an aqueous spore suspension of the mould from a potato–agar slope culture, incubated for 3–4 days at 32°C. and then at room temperature for 4–5 days more until spores just tinged with brown were obtained.

Aqueous solutions of various arsenic compounds, sterilized for 25–30 min. at 120°C., or alternatively, at 100°C. as indicated above, were added and the usual cotton-wool plugs replaced by rubber bungs carrying tubes lightly plugged with cotton-wool. These had been sterilized at 120°C. for 25–30 min. The flasks were arranged in series and a continuous stream of sterile air was passed through, volatile arsenic compounds being absorbed in Biginelli's solution (mercuric chloride in dilute hydrochloric acid, see page 318). Sterilized solutions of all arsenic compounds other than arsenious oxide were found to be free from inorganic arsenic. The average concentration of the arsenious oxide was 0.2–0.25 g., of sodium methylarsonate 1–1.5 g., and of the sodium cacodylate 0.1–0.3 g.

per 100 g. of fresh crumbs. The ethylarsonate was used in concentrations of 0.2–0.25 and 0.5 g. of the acid sodium and potassium salts, respectively, per 100 g. of crumbs.

When arsenious oxide was used, the precipitate (B_1) which formed in the acidified mercuric chloride solution had a melting point of 264°C. and was identical with Biginelli's second compound of melting point 270°C. On passage of the gas for some weeks, the melting point of the precipitate fell to about 221°C., recrystallization from hot water giving needles (B_2) of melting point 224–226°C.; these were also obtained when Gosio gas was passed into dilute Biginelli's solution.

A comparison of B_1 and B_2 with the precipitates obtained from Biginelli's solution with arsine, diethylarsine oxide, diethylarsine, and triethylarsine showed them to be entirely different and conclusively proved that Gosio gas could not be identical with any one of these compounds.

The properties of the mould gas are also different from those of monoethylarsine or monomethylarsine (74), which oxidize in air to form red solids.

Analyses of B_1 and B_2 proved that these compounds are the dimercurichloride and monomercurichloride of trimethylarsine, $(CH_3)_3As \cdot 2HgCl_2$ and $(CH_3)_3As \cdot HgCl_2$, and that Gosio gas is therefore trimethylarsine,[2] a volatile liquid of boiling point 53°C. which has long been known. Direct comparison confirmed this conclusion. Trimethylarsine with Biginelli's solution gave a precipitate identical with B_1, as shown by melting point, mixed melting point (265°C.), and all other properties. The mercurichloride precipitated with dilute Biginelli's solution melted at 224°C. and was identical with B_2 similarly obtained from Gosio gas.

When the arsenious oxide of the bread-crumb cultures was replaced by sterilized solutions of sodium methylarsonate, $CH_3AsO(ONa)_2$, or sodium cacodylate, $CH_3AsOONa$ (free from inorganic arsenic), the evolved gas gave a mercurichloride which was shown by melting point and mixed melting point to be identical with that obtained with arsenious oxide.

The identity of Gosio gas was then confirmed by several further observations:

[2] Trimethylarsine when kept in a tube with limited access of air gave, after 6 weeks, a white solid which on solution in alcohol and precipitation with ether gave cacodylic acid. The filtrate on treatment with picric acid yielded hydroxytrimethylarsonium picrate, indicating the formation of trimethylarsine oxide.

During the preparation of allyldimethylarsine (see page 322) a dilute ethereal solution was allowed to evaporate slowly. From the residual white solid cacodylic acid was isolated as in the case of trimethylarsine, and treatment of the filtrate with picric acid yielded allylhydroxydimethylarsonium picrate, $(CH_3)_2As(CH_2CH=CH_2)(OH)OC_6H_2(NO_2)_3$. Triethylarsine with limited access of air yields diethylarsonic acid, $(C_2H_5)_2AsOOH$ (95a).

Evans, Mann, Peiser, and Puride (83) suggest that trimethylarsine dimercurichloride may have double the normal molecular weight and that a probable formulation is
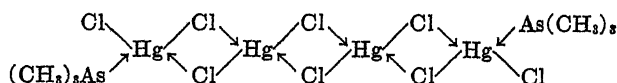
An alternative structure is also discussed by these authors.

(a) Compounds B_1 and B_2 with nitric acid gave hydroxytrimethylarsonium nitrate, $(CH_3)_3As(OH)NO_3$, shown by melting point and mixed melting point to be identical with the product obtained from the synthetic arsine and nitric acid or by passing Gosio gas into nitric acid. (b) Both these nitrates with sodium picrate gave hydroxytrimethylarsonium picrate, $(CH_3)_3\overset{+}{As}(OH)\overset{-}{O}C_6H_2$-$(NO_2)_3$. (c) Synthetic trimethylarsine and hydrogen peroxide gave trimethylarsine oxide, $(CH_3)_3AsO$, which with picric acid yielded the picrate (melting point and mixed melting point 218–219°C.). (d) Passage of Gosio gas through alcoholic benzyl chloride gave a quaternary salt and thence a picrate, shown by melting point and mixed melting point to be benzyltrimethylarsonium picrate, $(CH_3)_3\overset{+}{As}(CH_2C_6H_5)\overset{-}{O}C_6H_2(NO_2)_3$.

Since many aliphatic arsines are oxidized in air, it was necessary in order fully to establish the identity of Gosio gas (which is obtained in highly aerated cultures) to show that trimethylarsine can be volatilized unchanged in an air stream. On passage of air over or through the amyl ether–xylene solution obtained in the preparation of trimethylarsine (139) and then into Biginelli's solution, a precipitate was formed which had a melting point of 265°C. and gave a mixed melting point of 265°C. with substance B_1 obtained from similar treatment of Gosio gas.[2]

II. ALKYLARSONIC ACIDS AND *S. brevicaulis*

It seemed possible (i) that in the case of the formation of trimethylarsine from sodium methylarsonate and sodium cacodylate the mould might cause preliminary fission of the arsenic–carbon link, giving rise to inorganic arsenic. This could not, however, be detected at the close of the experiment, by extracting the bread crumbs and mycelium with hot water, filtering, acidifying, and treating with hydrogen sulfide. No arsenious sulfide was precipitated. There still remained the further possibility (ii) that in the methylarsonate and cacodylate experiments the trimethylarsine might have arisen by reduction, followed by dismutation:

$$CH_3AsO(OH)_2 \rightarrow CH_3As(OH)_2 \rightarrow CH_3AsO$$

$$3CH_3AsO = (CH_3)_3As + As_2O_3$$

and

$$(CH_3)_2AsOOH \rightarrow (CH_3)_2AsOH$$

$$3(CH_3)_2AsOH \rightarrow 2As(CH_3)_3 + As(OH)_3$$
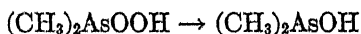
Grischkewitsch-Trochimovski's observation (109) that the action of alkali on chlorodiethylarsine gives triethylarsine and other compounds rendered it necessary to bear such a possibility in mind. He states, however, that cacodyl chloride, $(CH_3)_2AsCl$, gives the pure oxide with alkali.

It appeared therefore of importance to study the behavior of sodium ethylarsonate to cultures of the mould on sterile bread crumbs, and this was done. A garlic odor was again evolved and Biginelli's solution gave a solid (B_3) which depressed the melting point of the mercurichloride (B_1) obtained from the

methylarsonate cultures. B_3 was also obtained when synthetic ethyldimethyl-arsine, $(CH_3)_2AsC_2H_5$, was treated with Biginelli's solution (139).

The gas from the ethylarsonate cultures after passage through benzyl chloride yielded a picrate, identical with synthetic benzylethyldimethylarsonium picrate, $(CH_3)_2(C_2H_5)\overset{+}{A}s(CH_2C_6H_5)\overset{-}{O}C_6H_2(NO_2)_3$, prepared from ethyldimethylarsine and benzyl chloride. Absorption of the mould gas in nitric acid gave a nitrate and thence a picrate, identical with synthetic hydroxyethyldimethylarsonium picrate, $(CH_3)_2(C_2H_5)\overset{+}{A}s(OH)\overset{-}{O}C_6H_2(NO_2)_3$.

These results show that neither removal of an alkyl group according to (*i*) nor dismutation (*ii*) occurs, since in the first case trimethylarsine would have been obtained and in the second a mixture of trimethylarsine and triethylarsine. This reaction, involving both methylation and reduction to a derivative of trivalent arsenic, was then further studied (58, 63). By addition of (*a*) diethyl-arsonic acid, $(C_2H_5)_2AsOOH$, (*b*) *n*-propylarsonic acid, and (*c*) allylarsonic acid, $CH_2\!\!=\!\!CHCH_2AsO(OH)_2$, to similar cultures of the same strain of the mould in concentrations varying from 0.2 to 0.5 per cent, mixed methylated arsines were produced. These were removed in a sterile air stream, and absorbed in suitable reagents. From (*a*) methyldiethylarsine was obtained and converted to the dimercurichloride and to diethylhydroxymethylarsonium picrate. Similarly (*b*) gave dimethylpropylarsine (58), which was identified as the dimercurichloride, as benzyldimethylpropylarsonium picrate, and as hydroxydimethylpropylar-sonium picrate. Dimethylpropylarsine was also obtained (63) upon addition of methylpropylarsonic acid to bread cultures of *S. brevicaulis*. Under similar conditions ethylpropylarsonic acid gave ethylmethylpropylarsine, characterized by formation of the usual derivatives (63).

In an analogous manner (*c*) gave rise to allyldimethylarsine, $(CH_3)_2AsCH_2CH\!\!=\!\!CH_2$, which was characterized as the dimercurichloride and as allylbenzyl-dimethylarsonium picrate.

It is interesting that in spite of the powerful reducing action[3] exercised by *S. brevicaulis* the double bond of the allyl group in allylarsonic acid is unaffected, the melting points of the dimercurichloride and the benzylarsonium picrate from the resulting arsine being different from those of the corresponding *n*-propyl compounds.

III. *S. brevicaulis* AND INORGANIC COMPOUNDS OF SELENIUM

Attention was then turned to some early experiments of Rosenheim (183) in England in 1902, who showed that when *S. brevicaulis* was grown upon sterilized bread crumbs in the presence of inorganic compounds of selenium and tellurium, gaseous products possessing powerful and unpleasant odors were evolved. In

---

[3] In bread cultures of *S. brevicaulis* hydroxytrimethylarsonium nitrate (the nitrate of trimethylarsine oxide) and tri-*n*-propylarsine oxide are reduced to trimethylarsine and tri-*n*-propylarsine, respectively (60). The conversion of sodium arsenate and the salts of mono- and di-alkylarsonic acids to methylated tertiary arsines is clearly also a reduction (58, 60, 61, 63). Furthermore diethyl sulfoxide, $(C_2H_5)_2SO$, and hydroxydimethylsele-nonium nitrate (the nitrate of the selenoxide, $(CH_3)_2Se(OH)NO_3$) are converted by bread cultures of the mould to diethyl sulfide and dimethyl selenide, respectively (62).

the case of tellurium the smell resembled that of Gosio gas, but with selenium a characteristic and quite different odor was produced. The substances responsible for the odors were not identified. Maassen (152), working in Berlin almost simultaneously, obtained analogous results and, as the result of decidedly insufficient experimental work based entirely on odor, stated that the volatile products consisted of diethyl selenide and diethyl telluride. He also superficially examined the expired air of animals which had received injections of soluble inorganic selenites and tellurites and concluded that in these cases the unpleasant odor of the breath was due to dimethyl selenide and dimethyl telluride. A similar conclusion on equally unsatisfactory evidence had been reached as regards animals injected with tellurium compounds by Hofmeister (127) in 1894. Maassen concluded therefore that the animal body deals differently with compounds of selenium and tellurium than the organism of the mould. This statement has been fairly frequently quoted. It is clear that in deciding that the gas from the selenium or tellurium mould cultures was an ethyl derivative, Maassen was somewhat unduly influenced by Biginelli's incorrect identification of Gosio gas as diethylarsine, a report which had been published one year previously (24).

The formation of odorous compounds in the breath of animals treated with inorganic derivatives of tellurium was first observed by Gmelin (99). Hansen (117), on administration on five successive days of potassium tellurite to dogs or men, detected a garlic odor, similar to that of diethyl telluride, in the breath after a few minutes. This lasted for weeks and the persons in question were obliged to forsake the society of their fellows. A similar effect was observed by Japha (137) with inorganic selenium compounds. The odors have also been attributed to hydrogen telluride or selenide. Other references to the same phenomenon in human subjects have been recorded from time to time, but neither in the case of "selenium breath" nor "tellurium breath" was the odorous substance satisfactorily identified.

The gas evolved from the cultures in Rosenheim's early experiments with selenium compounds has now been identified (62). The volatile product arising from several pure cultures of two different strains of S. brevicaulis on sterile bread crumbs in the presence of either sodium selenate or sodium selenite was separately aspirated in a stream of sterile air through (a) Biginelli's solution, (b) mercuric bromide, (c) nitric acid, (d) potassium platinochloride, and (e) benzyl chloride. The products obtained were: in (a) dimethyl selenide mercurichloride, $(CH_3)_2Se \cdot HgCl_2$; in (b) dimethyl selenide mercuribromide; in (c) hydroxydimethylselenonium nitrate, $(CH_3)_2Se(OH)NO_3$; in (d) dimethyl selenide α-platinochloride, $PtCl_2 \cdot 2(CH_3)_2Se$ (95b); and in (e) benzyldimethylselenonium chloride, $(CH_3)_2Se(CH_2C_6H_5)Cl$, isolated as the picrate. Diethyl selenide mercurichloride was also prepared and found to be different from the mould product. The mould gas is therefore dimethyl selenide.

IV. S. brevicaulis AND INORGANIC COMPOUNDS OF TELLURIUM

Reference has already been made to the observations of earlier workers on the production of a garlic odor resembling that of an alkyl telluride when potassium

tellurite is administered orally to men or animals or added to cultures of *S. brevicaulis*. Blyth (33) refers to the case of a student who swallowed "a dose of tellurium" and had to be segregated. He also mentions the phenomenon of "bismuth breath," formerly well known to pharmacists and attributed to the presence of traces of tellurium in medicinal preparations of bismuth. Further details are given by Brownen (36), Letts (147), and Reissert (179). During a recent investigation of inorganic derivatives of tellurium in Leeds the odor could easily be detected in the vicinity of those engaged in the work, although they had never come into contact with organic compounds of tellurium.

On the basis of work which is discussed in an earlier paper (62), Maassen (152) concluded that the animal body elaborated dimethyl selenide and dimethyl telluride, and *Scopulariopsis brevicaulis* the corresponding diethyl derivatives. (Maassen's conclusion is incorrectly quoted in *British Chemical Abstracts* (35) and by Mellor (155), the contrary view being attributed to him.) In the case of the mould and sodium selenite and selenate this was disproved by Challenger and North (62), the product from cultures on bread or glucose-Czapek-Dox medium being shown to be dimethyl selenide. Difficulty was, however, experienced with similar cultures containing potassium tellurite. Aspiration of the volatile products through Biginelli's solution (mercuric chloride in dilute hydrochloric acid) gave traces of precipitate which decomposed without melting. Other absorbents gave equally unsatisfactory results.

Several factors appeared to contribute to this lack of success. Soluble tellurites are readily reduced to black amorphous tellurium by cultures of the mould. Maassen (152) states that this is unavailable for conversion into the volatile product, a conclusion confirmed by Blackburn in Leeds (56). Furthermore, the alkyl tellurides readily undergo atmospheric oxidation, giving complex products (13, 205).

Success was at last achieved (25) by growing *S. brevicaulis* upon bread crumbs in test-tubes and absorbing the volatile product in about 5 cc. of Biginelli's solution or other reagent. In this way contact of the mould gases with large volumes of air was somewhat diminished and dimethyl telluride mercurichloride (50) was obtained.

With sodium hydroxide the mercurichloride gave mercury and soluble dimethyl telluride dihydroxide or oxide or a compound of this with some other methyl derivative of tellurium (compare reference 13). The alkaline solution with hydrobromic acid gave dimethyl telluride dibromide, melting point 94-95°C. (204), thus confirming the identification of the mould gas. Furthermore, by absorption in alcoholic iodine, dimethyl telluride diiodide (melting point 125°C. with decomposition) was obtained. The recorded melting points of the dibromide (24°C.) and diiodide (57°C.) of diethyl telluride (151) differ widely from those of the corresponding dimethyl derivatives.

The mould gas is therefore dimethyl telluride, and Maassen's statement (152) that it consists of the diethyl compound is incorrect. This conclusion was also confirmed by the use of cultures on 2 per cent glucose-Czapek-Dox medium. The behavior of tellurium compounds in cultures of *S. brevicaulis* thus falls into

line with that of inorganic derivatives of arsenic (61) and selenium (62). It is of interest that arsenic resembles selenium and tellurium in its toxicological properties much more than it resembles antimony (70).

In order to discover whether the deposition of tellurium in tellurite cultures of *S. brevicaulis* was due to a reducing action of the bread or of some product elaborated by the mould, bread crumbs moistened with a tellurite solution were left in a corked test-tube. Practically no deposition of tellurium occurred, but after some days a green mould appeared and a strong odor of dimethyl telluride was noticed. A culture of this organism was sent to Dr. Thom of the United States Department of Agriculture, Washington, through the courtesy of Dr. St. John Brooks of the Lister Institute, who stated: "I place the organism near *P. notatum*, not necessarily identical with Westling's strain of *P. notatum*, since biochemical differences between strains are the rule rather than the exception."

Bread cultures of the "green mould" containing tellurite were then examined, and the evolved dimethyl telluride identified as before and as benzyldimethyl-telluronium picrate. There was only very slight formation of tellurium, which would appear to be the special advantage of this particular organism. Dimethyl telluride was also produced in cultures on 2 per cent glucose-Czapek-Dox medium.

In view of Dr. Thom's results, pure cultures of *P. chrysogenum* Thom (Washington 26) and *P. notatum* were obtained from the Lister Institute. In bread–tellurite cultures the former gave dimethyl telluride, identified as the mercuri-chloride and the dibromide, but only a very faint odor could be observed when *P. notatum* was used. Both organisms readily gave dimethyl selenide in bread cultures containing sodium selenite or selenate. This was also produced in bread–selenate cultures by the "green mould." (For the behavior of these three organisms with salts of alkyl seleninic acids, $RSeO_2Na$, see page 343.)

None of these green *Penicillia* give any odor of trimethylarsine in bread cultures containing arsenious acid,[4] but all convert sodium methylarsonate in bread cultures to trimethylarsine, which is also produced in similar cultures of *P. chrysogenum* and *P. notatum* containing sodium cacodylate (26). Here, although dismutation appears improbable (see page 321), it must be conceded that methyl groups are present in the substrate. It is therefore interesting to note that bread cultures of *P. chrysogenum* convert sodium allylarsonate to allyldimethylarsine, $CH_2{=}CHCH_2As(CH_3)_2$ (26).

V. COMPARISON OF THE ACTION OF LIVING ORGANISMS ON COMPOUNDS OF ARSENIC, SELENIUM, AND TELLURIUM

Bearing in mind the methylating powers of the animal body (59, 62) there can be no doubt that men and animals also evolve dimethyl telluride after administra-

---

[4] Later experiments by Mr. P. T. Charlton (June, 1944) indicate that bread cultures of *P. notatum* containing approximately 0.2, 0.3, and 0.4 per cent of arsenious oxide evolve faint garlic odors, recognizable with difficulty. Lower concentrations were without effect. The other two *Penicillia* again failed to produce any garlic odor with concentrations of arsenious oxide ranging from 0.02 to 0.4 per cent. Further work is in progress.

tion of tellurium. This has already been stated both by Hofmeister (127) and by Maassen (152), but their conclusions, which have been widely quoted, were based on considerations of odor and there exists no proof of the nature of the alkyl telluride evolved by experimental animals.

Dudley (76) refers to the garlic odor of the breath of persons suffering from selenium poisoning and to the presence of a volatile, ether-soluble selenium compound in the urine of a horse after ingestion of sodium selenite. As concluded by Challenger and North from analogous experiments with *S. brevicaulis* (62), the exhaled product is almost certainly dimethyl selenide.

It would therefore appear that arsenic also should be methylated in the animal body and exhaled as trimethylarsine. That no odor comparable in intensity to that produced by tellurite follows administration of medicinal doses of inorganic compounds of arsenic is well known (see also Reissert (179)), but occasional references to the presence of a garlic odor in the perspiration following upon arsenical poisoning occur (34).

Pleschtizer and Preobrajensky (172) passed the breath from patients in receipt of inorganic arsenic through bromine water. Treatment with ammonia followed by evaporation gave a slight residue in which the presence of arsenic was detected by addition to cultures of *S. brevicaulis*, the garlic odor of Gosio gas being obtained. The presence of some volatile compound of arsenic in the breath was thus rendered extremely probable, but the quantity was too small for identification. These authors, at that time unaware of the identification of Gosio gas as trimethylarsine (61), merely quoted Biginelli's statement (24) that it consists of diethylarsine.

Keeser (140), however, while citing this latter work, states without further comment that according to the Russian workers the gas from cultures of *S. brevicaulis* on arsenical media is diethylarsine and not trimethylarsine, thus unintentionally creating a wrong impression.

Carlson (49), Montgomery (158), and Puntoni (176) refer to the production of a garlic odor in the breath after ingestion or injection of cacodylic acid or its sodium salt. Bloemendal (31) passed the exhaled air of a rabbit which had received 20 mg. of sodium cacodylate through alkaline potassium permanganate solution, which then contained arsenic. The odorous product was not identified. Montgomery suggested that it was cacodyl. From the behavior of sodium cacodylate in cultures of *S. brevicaulis* (61), the formation of trimethylarsine would be expected by reduction and further methylation. However, methylation does not occur readily in animals receiving arsenious oxide (see above), and trimethylarsine, if formed from cacodylic acid in the animal body, might conceivably arise by reduction and dismutation.

$$(CH_3)_2AsOOH \xrightarrow{\text{reduction}} (CH_3)_2AsOH$$
$$3(CH_3)_2AsOH = 2As(CH_3)_3 + As(OH)_3$$
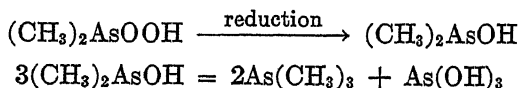
(See page 321 and compare the action of chlorodiethylarsine with alkali; 109, see also 12.) Such dismutations are well established in the case of the alkyl

derivatives of tellurium (75).   As shown on page 322, however, aliphatic arsonic acids other than the methyl compounds do not undergo dismutation in mould cultures.   The mechanism by means of which methylarsonic acid and cacodylic acid yield trimethylarsine in mould cultures cannot be rigidly established, but by analogy with other alkylarsonic acids dismutation appears very improbable.

Puntoni attributed the garlic odor after oral administration of cacodylate to the effect of intestinal organisms, some of which he cultivated on cacodylate media, obtaining a similar odor.   Using strains of the same and two other bacteria, Challenger and Higginbottom (60) were unable to detect any odor in media containing arsenious oxide, sodium arsenate, sodium methylarsonate, or sodium cacodylate.   Many bacterial species were tested by Abel and Buttenberg (4), Hildebrandt (123), Sanger (186), Huss (136), and Emmerling (82), and also by Simons in the author's laboratory (192), but in no case was a garlic odor obtained in cultures containing arsenious oxide.   Gosio (104, 105) studied the behavior of inorganic tellurites and selenites in cultures of numerous bacteria and frequently observed reduction to the free element, but makes no mention of any odor arising from the cultures.   Maassen (152), however, states that eighteen species of bacteria, including many pathogenic forms, can give odorous products in the presence of soluble compounds of selenium and tellurium, especially when a good growth is obtained.   He recommends the use of an 18–20 hr. old agar culture and the addition of a sterile solution of sodium selenite or potassium tellurite (0.005 g. in 0.2 to 0.5 cc. of water) followed by an equal volume of bouillon.   After incubation of the material for 24 hr. at 30–35°C. he observed a strong odor.   Some bacteria employed by Maassen were tested by Simons (192) under similar conditions in the presence not only of arsenious acid but also of sodium methylarsonate, sodium cacodylate, and sodium selenite, but no odor was obtained.

The weight of the evidence would indicate that bacteria are unable to produce volatile methyl derivatives of arsenic, selenium, and tellurium, the statements to the contrary being based on observations of odor only.

Negative results were also obtained by Emmerling (82) and Huss (136), using various yeasts.   Challenger and Higginbottom (60) cultivated *Saccharomyces cerevisiae*, *S. carlsbergensis*, *S. monacensis*, and "Rasse XII" on beer-wort or 5 per cent glucose mineral salt solution in the presence of arsenious oxide, but no garlic odor was produced.   Verona (206) refers to a volatile arsenical product detected in very small quantity in cultures of the yeast *Saccharomyces ellipsoideus* Hansen, containing arsenic.   Dr. C. Simons, working in the author's laboratory, was unable to confirm this statement with the particular strain of this yeast available to him.

VI. ARSENIC-TOLERANT MOULDS

Reference may here be made to some observations which, although not concerned with biological methylation, possess certain superficial analogies with the subject.   In a paper which has already been cited, Thom and Raper (202) state that fungi which volatilize arsenic and also arsenic-tolerant organisms are

more numerous than was previously supposed. These tolerant organisms survive in arsenical media without decomposing the arsenic compound or producing volatile odorous products.

Further examples of this were recorded by various pharmacists in 1932. About that time the *British Pharmacopoeia* had modified the composition of Liquor Arsenicalis B.P. by omitting the Compound Tincture of Lavender and altering the pH. This change was soon followed by several letters to the *Pharmaceutical Journal* stating that a mould growth had appeared in specimens of the Liquor prepared according to the new formula. The first of these, by Sheard and Tribley, may be quoted:

"We have prepared several batches of Liquor Arsenicalis B.P. 1931 and find that if prepared with ordinary unsterilised distilled water, the solution rapidly develops extensive colonies of moulds of the Mucor type and also smells most foul in less than a week after preparation. If, however, the solution is sterilised by any of the customary methods no moulds, of course, develop. We conclude that Liquor Arsenicalis B.P. 1932 which has a p_H approximating to 7 is much more prone to the growth of moulds than the corresponding acid and alkaline solutions of arsenic of the B.P. 1914, and that it should be recently prepared, sterilised and carefully stored."

These statements were confirmed by Bennett (18, 19), who found that the most satisfactory pH for Liquor Arsenicalis is below 2 or above 9. Hampshire (115) stated that specimens of the new Liquor had been prepared which had kept satisfactorily for 12 months and suggested that "pharmacists should look carefully into their methods of making the Liquor."

Moore (159) identified one of the fungi:

At a recent meeting of the Science Section of the Birmingham Pharmaceutical Association a locally prepared sample of Liquor Arsenicalis B.P. 1932 was exhibited, which showed an abundant grey-black growth. On investigation this was found to be the common mould, *Cladosporium herbarum* (Link.), a member of the Hyphomycetes. This fungus is somewhat variable in form, but always possesses a well-branched mycelium which buds-off conidia, usually unicellular, but sometimes with a median septum; in a moist medium the conidia produce globose spores. All stages of the fungus were found in the sample examined. *Cladosporium herbarum* is a fungus of wide occurrence, growing saprophytically on a variety of substrata. It is known to occur on damp walls, especially of wine cellars, where it also occurs on casks; it has even been known to penetrate the corks of wine bottles in storage. It may be a factor in the blackening of cheese, contamination occurring in the dairy. It has also been reported as causing putrefaction in stored eggs, the conidia passing through the untreated shell and the lining membrane, then germinating to produce a mycelium in the "white." It is common in water supplies: Bewley and Budden, investigating the fungus flora of greenhouse water supplies from wells, tanks, brooks, and ponds, found *Cladosporium* present in thirty-four of forty-one samples. Salacz found *Cladosporium herbarum*, amongst other fungi, to be capable of growth and spore-formation in solutions containing 2 per cent. arsenic, and that growth would continue so long as the percentage did not exceed 4, above which the solution became lethal. Work on the physiology of this fungus and on various points arising from its occurrence in Liq. Arsenicalis is now in progress.

The reference to the odor suggested to the author that possibly the mould or moulds in question might be producing trimethylarsine and that the necessary organic matter might be introduced by accidental contamination.

A bottle of Liq. Arsenicalis B.P. 1932, in which a mould growth had formed at the bottom was obtained through the courtesy of Messrs. Goodall, Backhouse, and Co., Leeds. The solution had an odor which could not be identified, but was not that of trimethylarsine. A specimen of the growth was removed by Miss C. Higginbottom and inoculated on to sterilized slants of (a) potato–agar, (b) wort–agar, and (c) meat extract agar. Growth occurred, and (after a preliminary purification had been made on the same medium) a few spores from a potato–agar plate were inoculated on to sterile bread crumbs, as in the experiments of Challenger, Higginbottom, and Ellis (61). Growth occurred slowly at 28°C., and after 3 days arsenious oxide solution was added in quantity sufficient to give a concentration in the bread of about 0.2 per cent. Incubation was continued, but not the slightest garlic odor was developed by the culture, even after 10 days, the behavior being entirely different from that of the true "arsenical moulds" employed by Challenger and his collaborators. It should be borne in mind, however, that in these preliminary experiments no claim is made that the mould obtained from Liquor Arsenicalis was isolated in pure culture. Furthermore, Challenger inoculated samples of sterile Liq. Arsenicalis B.P. 1932 with pure cultures of S. brevicaulis. No germination occurred after several weeks and no odor developed. This work has been summarized by Dyer (78).

Further details were published by Milne and Rattray (156, 157). The growths from several samples of the Liquor were compared with S. brevicaulis, no resemblance being noted. The moulds appeared to be species of Fusarium and Torula and an organism which was not identified.

Samples of the Liquor adjusted to different pH values were inoculated with Rhizopus nigricans, Aspergillus glaucus, "Penicillium glaucum," and S. brevicaulis and left at room temperature and at 32°C. No definite increase in growth took place, although in the case of the samples at about pH 7 the moulds appeared to be healthiest, "but growth at best is slight." It may be mentioned that these authors refer to the "musty" odor of three different samples of the infected Liquor but do not mention any odor of garlic.

It is clear, therefore, that the organisms concerned with these observations are not true "arsenic organisms," i.e., they do not volatilize the arsenic, and that the odor is not due to trimethylarsine. The results appear, however, worthy of mention if only to avoid any possible confusion.

VII. FISSION OF THE DISULFIDE LINK IN $C_nH_{2n+1}S$—SC_nH_{2n+1} BY S. brevicaulis AND METHYLATION OF THE $C_nH_{2n+1}S$ GROUP

In view of the successful experiments with selenium and tellurium, attempts were made to obtain dimethyl sulfide by addition of sulfur or certain of its compounds to bread cultures of two different strains of S. brevicaulis. Negative

results were obtained with sulfur, sodium sulfite, sodium thiosulfate, sodium tetrathionate, thiourea, thiodiglycolic acid and its sodium salt, sodium formaldehydesulfoxylate (Rongalite), and also with sodium ethanesulfonate and ethanesulfinite, the last-named compound in liquid cultures.

This was somewhat surprising in view of the experiments of Pohl (173), who noticed a leek-like odor in the expired air of animals receiving subcutaneous or intravenous injections of thiourea. The odorous product was non-reactive to sodium hydroxide or mercuric cyanide, and was therefore not an alkylthiol. It was, however, absorbed by sulfuric acid and gave a precipitate with mercuric chloride which, on oxidation, yielded a sulfate. Pohl therefore concluded that the product was an alkyl sulfide. Hofmeister (127) was unable to detect any odor in the expired air of dogs and rabbits fed with powdered sulfur or injected with sodium sulfide or thiosulfate.

Neuberg and Grosser (167) stated that the precursor of the diethyl sulfide which was shown by Abel (3) to be evolved on warming the urine of dogs with alkali is diethylmethylsulfonium hydroxide. They also state that administration of diethyl sulfide to dogs gives rise to this compound, but experimental details have not been published.

Particular interest attaches to the observation of Haas (114) that the seaweeds *Polysiphonia fastigiata* and *P. nigrescens* evolve dimethyl sulfide shortly after being gathered. The occurrence in nature of methylated compounds of sulfur such as cheirolin, $CH_3SO_2CH_2CH_2CH_2N=C=S$, erysolin, $CH_3SO_2CH_2CH_2-CH_2CH_2N=C=S$ (see 9 for references), and particularly methionine, $CH_3-SCH_2CH_2CH(NH_2)COOH$, demonstrates the possibility of a biological methylation of sulfur. The relation of methionine to cysteine and to cystine suggested that compounds containing the —SH or —S—S— links might be more amenable to the methylating action of the mould.

Neuberg and Schwenk (168) showed that, on addition to a solution of sugar undergoing fermentation by bottom yeast, diethyl disulfide is reduced to ethylthiol.

Dr. H. E. North (unpublished observation) found that on addition of diethyl disulfide to bread cultures of *S. brevicaulis* ethylthiol was evolved; it was identified as the mercaptide, $Hg(SC_2H_5)_2$, by absorption in mercuric cyanide. The gases issuing therefrom reacted with mercuric chloride, giving a precipitate which was clearly a mixture. Diethyl disulfide, boiling point 153°C., is volatile in a stream of air and, as it is inert to mercuric cyanide, any which escaped reaction in the culture flasks would reach the mercuric chloride.

Morin (160) and Otto (169) mention the formation of a heavy white crystalline precipitate from diethyl disulfide and alcoholic mercuric chloride, but give no further details.

The behavior of aliphatic disulfides RSSR (R = C_2H_5 or n-C_3H_7) with excess of saturated aqueous mercuric chloride was therefore examined. In each case a white precipitate of the composition $RSHgCl \cdot HgCl_2$ was formed. Its weight accounted for only about 70 per cent of the disulfide, the remainder having formed
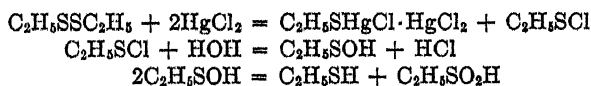
soluble products.[5] The insoluble compounds were shown by analysis, melting points, and mixed melting points with compounds of known composition to be identical with the compounds obtained from the corresponding alkylthiols and excess of aqueous mercuric chloride. Bertram (22) obtained CH_3SHgCl from methylthiol. The product formed from ethylthiol in alcoholic solution is stated by Débus (73) to be C_2H_5SHgCl, but no mention of a double compound with mercuric chloride is made. Sachs (185), however, states that with mercuric chloride in ether C_2H_5SHgCl is converted into $C_2H_5SHgCl \cdot HgCl_2$. The same addition takes place slowly in aqueous solution.

Since the compounds RSHgCl or $RSHgCl \cdot HgCl_2$ would clearly be formed in the mercuric chloride absorption bottles during experiments with the mould and RSSR, their properties were studied. Neither of these compounds liberates any thiol when warmed with sodium hydroxide in an air stream, aspiration through mercuric cyanide giving no precipitate. The mercurichlorides of the alkyl sulfides readily eliminate R_2S under these conditions.

VIII. S. brevicaulis AND DIALKYL DISULFIDES

The behavior of disulfides toward mercuric chloride having been established, ethyl and n-propyl disulfides were added in dilute aqueous suspension to the bread cultures. In every case the products issuing from the culture flasks consisted of the alkylthiol, RSH, the unchanged disulfide, RSSR, and the methyl alkyl sulfide, $RSCH_3$. In the case of the relatively non-volatile di-n-propyl disulfide very little of this came over. The precipitates in the mercuric chloride flasks consisted of mixtures of the mercuric chloride addition product of the methyl alkyl sulfide with varying amounts of $RSHgCl \cdot HgCl_2$. On treatment of these mixtures with sodium hydroxide in a slow stream of air, pure methyl alkyl sulfide was evolved and converted to the mercurichloride. No alkylthiol volatilized under these circumstances (see above). The methyl alkyl sulfides were also characterized as the benzylmethylalkylsulfonium picrates, and (in the case of ethyl methyl sulfide) as the double compound with platinous chloride.

[5] It was suggested by Challenger and Rawlings (64) that, in the case of diethyl disulfide, the soluble product might be ethanesulfinic acid, $C_2H_5SO_2H$, arising from the chlorothiol. C_2H_5SCl, by way of the sulfenic acid, C_2H_5SOH, which then undergoes dismutation:

$$C_2H_5SSC_2H_5 + 2HgCl_2 = C_2H_5SHgCl \cdot HgCl_2 + C_2H_5SCl$$
$$C_2H_5SCl + HOH = C_2H_5SOH + HCl$$
$$2C_2H_5SOH = C_2H_5SH + C_2H_5SO_2H$$

The sulfinic acid was later isolated by Blackburn and Challenger (56) through the sodium salt as ethyl p-nitrobenzyl sulfone. The fission of dimethyl disulfide by mercuric chloride is similar and the methanesulfinic acid was identified as methyl p-nitrobenzyl sulfone. The intermediate sulfenic acid (RSOH) could, of course, arise directly by incipient hydrolytic fission thus:

$$R_2S_2 + HOH = RSH + RSOH$$

the thiol being removed as the very insoluble $RSHgCl \cdot HgCl_2$. Such fission was demonstrated for diethyl disulfide and water at 170°C. (64).

In view of the reducing properties of cultures of *S. brevicaulis* (58, 59), the formation of thiols from the disulfides was not surprising. Addition of ethylthiol and *n*-propylthiol to bread cultures of the mould under the same conditions as obtained for the disulfides gave very similar results, methylation being observed in each case.

The reaction was also extended by Blackburn and Challenger (56) to di-*n*-butyl and di-*n*-amyl disulfides, which in bread cultures of the mould are converted to *n*-butylthiol and *n*-butyl methyl sulfide and to *m*-amylthiol and *n*-amyl methyl sulfide, respectively. These were removed, separated, and identified as in the case of the ethyl and *n*-propyl derivatives. Here again the amount of methyl and alkyl sulfides is larger than that of the alkylthiols, but the total yield is very low. With diethyl disulfide as substrate much passes over unchanged and, as already stated, the product $C_2H_5SHgCl \cdot HgCl_2$ accompanies the ethyl methyl sulfide mercurichloride, $CH_3SC_2H_5 \cdot 2HgCl_2$. The di-*n*-propyl disulfide is less volatile and very little reaches the mercuric chloride. This is still more obvious with di-*n*-butyl and di-*n*-amyl disulfides, the methyl alkyl sulfide mercurichloride being entirely free from chloromercury alkylthiol derivatives. The fission of the disulfide link by *S. brevicaulis* appears therefore to be a general reaction of the simple aliphatic disulfides.

This biological conversion of *n*-butyl disulfide to the corresponding thiol is of interest in view of the occurrence of these two compounds and of isoamylthiol in the anal secretion of the skunk (6, 17). Traces of methylthiol are also stated to be present.

Earlier workers also considered that the higher homologues of methylthiol were contained, along with basic nitrogenous compounds, in the secretions of various animals allied to the skunk. References are given by Nencki and Sieber (166). Furthermore the secretion of the zorrino, a South American marten, appears to contain a thiol with four atoms of carbon and probably the corresponding disulfide (85).

It was at first uncertain whether di-*n*-butyl and di-*n*-amyl disulfides would volatilize from the cultures and react with the mercuric chloride in the absorption bottles. Their behavior toward this reagent was therefore studied in water for the butyl compound and in alcohol in the case of di-*n*-amyl disulfide. The products were chloromercury *n*-butylthiol, C_4H_9SHgCl, and chloromercury *n*-amylthiol, respectively. Unlike the fission products of the first three dialkyl disulfides (57), these contain no coördinated molecule of mercury chloride.

At the commencement of this account of the biological formation of methyl derivatives of sulfur it was stated that numerous inorganic sulfur compounds failed to undergo methylation in cultures of *S. brevicaulis*. It is therefore particularly interesting to refer to the work of Birkinshaw, Findlay, and Webb (27), who have recently shown that the wood-destroying fungus *Schizophyllum commune*, Fr., when grown on an aqueous medium containing glucose, inorganic salts, and a trace of "Marmite," converts inorganic sulfate to methyl mercaptan, CH_3SH. This was absorbed in mercuric cyanide and chloride and characterized as mercury dimethylthiol, $(CH_3S)_2Hg$, and chloromercury methylthiol,

CH_3SHgCl, respectively. Traces of hydrogen sulfide are probably formed, but no dimethyl sulfide. This is the only recorded instance of the biological methylation of inorganic sulfur (compare 64). It will be recalled that *S. brevicaulis* forms dimethyl selenide, but no selenothiol, CH_3SeH, from selenate or selenite.

IX. BEHAVIOR OF THIOUREA AND SIMILAR COMPOUNDS IN THE HUMAN BODY

Pohl's experiments on the production of a leek-like odor in the expired air of animals receiving thiourea, which were described at the commencement of Section VII, have lately acquired an enhanced interest. During the last two years thiourea has found application in the treatment of thyrotoxicosis (hyperthyroidism) arising from an excessive secretion of thyroxine by the thyroid gland (10, 11, 125). Good results have been obtained, but a minor disadvantage is the peculiar sweetish odor which is imparted to the breath. The author is much indebted to Dr. C. A. Mawson of the Pathology Department, Royal Berkshire Hospital, Reading, for drawing his attention to this phenomenon. Dr. Mawson and his colleagues compare the odor to that of seaweed (*cf.* 114).

2-Thiouracil (I), which is also employed in the treatment of thyrotoxicosis, does not give rise to this odor. In view of the close relation of this uracil to thiourea, this difference is remarkable. It would appear as if thiourea is not produced, at any rate in quantity, from thiouracil in the organism.

$$
\begin{array}{cccc}
\text{N—CH} & \text{NH} & \text{N——CO} & \text{N—C=CHC}_6\text{H}_5 \\
\| \quad \| & \| & \| \quad | & \| \\
\text{HSC} \quad \text{CH} & \text{CSH} & \text{HSC} \quad \text{CH}_2 & \text{HSC} \\
| \quad | & | & | \quad | & | \\
\text{N=COH} & \text{NH}_2 & \text{NH—CO} & \text{N=COH} \\
\text{I} & \text{II} & \text{III} & \text{IV} \\
\text{2-Thiouracil} & \text{Thiourea} & \text{2-Thiobarbituric} & \text{5-Benzalthiohydantoin} \\
& & \text{acid} &
\end{array}
$$
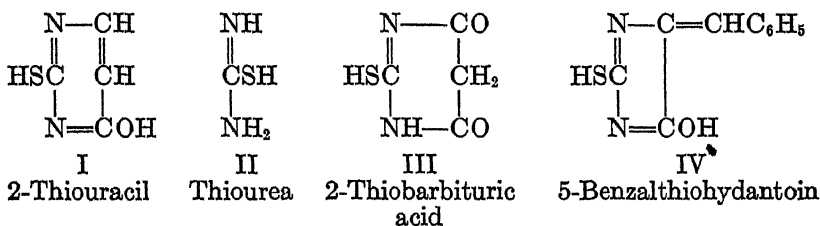
Astwood (10, 11) found that the antithyroid activity of 2-thiouracil (I), 2-thiobarbituric acid (III), *sym*-diethylthiourea, and 5-benzalthiohydantoin (IV) is greater than that of thiourea (II).

In view of the work of Haas, of Rawlings, and of Blackburn (see above) it would appear probable that the odor is due to methylthiol or to dimethyl sulfide, probably the latter. Experiments are at present in progress in collaboration with Dr. Mawson and with Dr. Leese of the Leeds General Infirmary with the object of identifying the odorous compound.

X. THE MECHANISM OF BIOLOGICAL METHYLATION

A. The acetic acid hypothesis

The first of the suggested mechanisms (59) might proceed thus in the case of arsenious acid:

$$As(OH)_3 + 3CH_3COOH = As(CH_3)_3 + 3CO_2 + 3H_2O$$
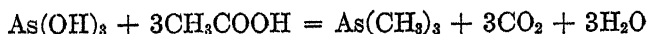
Such a reaction would be analogous to the well-known cacodyl oxide test. Alternatively, arsonoacetic acid might result by a process of dehydrogenation:

$$HOOCCH_2 \cdot H + H \cdot AsO(OH)_2 = 2H + HOOCCH_2AsO_3H_2$$
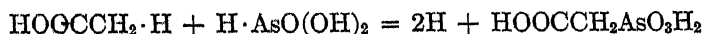
This by loss of carbon dioxide might yield methylarsonic acid, $CH_3AsO(OH)_2$, which, on reduction to $CH_3As(OH)_2$, isomerization to $CH_3AsO(OH)H$, and renewed reaction with acetic acid, could finally yield trimethylarsine. The suggested dehydrogenation would be analogous to the formation of succinic acid from calcium acetate by *Mucor stolonifer* (47).

Challenger and Higginbottom (59) were unable to obtain any supporting evidence for this hypothesis; arsonoacetic acid in bread cultures of *S. brevicaulis* gave small quantities of trimethylarsine in some, but not all, experiments; α-arsonopropionic acid gave traces of this arsine, probably owing to the formation of a little arsenious acid which is readily eliminated from compounds of this type. Decarboxylation would have yielded ethylarsonic acid, which in the presence of the mould would have been converted to ethyldimethylarsine; this was not observed. Using α-arsonobutyric acid in bread cultures of *S. brevicaulis*, Challe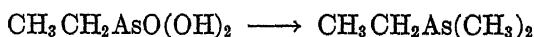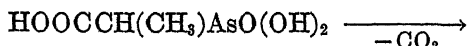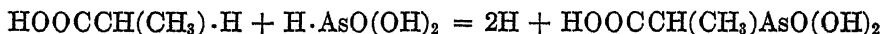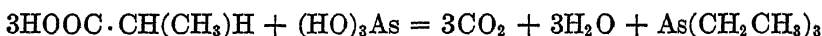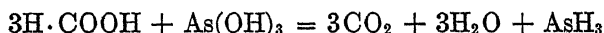nger and Rawlings (63) observed neither trimethylarsine nor n-propyl-dimethylarsine in two experiments, each lasting 42 days. Moreover, only pure trimethylarsine was evolved from cultures containing arsenious acid with salts of formic, propionic, and butyric acids, whereas on the acetic acid hypothesis some formation of hydrogen arsenide, triethyl- and tri-n-propylarsines, or even of mixed methylalkylarsines might conceivably have been expected, e.g.:

$$3H\cdot COOH + As(OH)_3 = 3CO_2 + 3H_2O + AsH_3$$

$$3HOOC\cdot CH(CH_3)H + (HO)_3As = 3CO_2 + 3H_2O + As(CH_2CH_3)_3$$

$$HOOCCH(CH_3)\cdot H + H\cdot AsO(OH)_2 = 2H + HOOCCH(CH_3)AsO(OH)_2$$

$$HOOCCH(CH_3)AsO(OH)_2 \xrightarrow[-CO_2]{}$$

$$CH_3CH_2AsO(OH)_2 \longrightarrow CH_3CH_2As(CH_3)_2$$

It may be mentioned that thiodiglycolic acid $(HOOCCH_2)_2S$ gave no dimethyl sulfide. These results suggest that decarboxylation of the group $>\!CHCOOH$ does not readily occur in cultures of *S. brevicaulis*.

B. The formaldehyde hypothesis

The view that methylation in green plants is effected by formaldehyde is generally accepted by chemists. Emde (81) differentiates between "primary" formaldehyde produced by photosynthesis and that arising by "secondary" breakdown processes. In moulds and animals any formaldehyde involved in methylation reactions is presumably of secondary origin and even in plants some may arise by the demethylation of NCH_3 groups (or in other ways, see pages 338, 339) and become again available for methylation (see 110, 122, 182). Numerous methylations can be effected by formaldehyde (see Hess (119) for summary, also Werner (214); Clarke, Gillespie, and Weisshaus (68)). The presence of an oxygen acceptor is, of course, necessary. As will be seen later this may be either formaldehyde itself, formic acid, or a suitable group present in the molecule of the compound undergoing methylation.

It has unfortunately not been possible to apply successfully a crucial test to the formaldehyde hypothesis as regards the methylations effected by moulds. In its application to the production of trimethylarsine, this postulates the formation of hydroxymethylarsonic acid, $HOCH_2AsO(OH)_2$, as the first stage, followed by reduction to methylarsonic acid. After further reduction to $CH_3As(OH)_2$, the isomeric form, $CH_3AsO(OH)H$, might be expected to react again with formaldehyde (59, 61), repetition of the process yielding cacodylic acid, $(CH_3)_2AsOOH$, and finally trimethylarsine. Hydroxymethylarsonic acid could not be synthesized and its homologue, $HOCH_2CH_2AsO(OH)_2$, when purified from traces of inorganic arsenic, is inert in bread cultures of the mould or, at least, gives no volatile product. Had reduction of the β-hydroxyl group occurred in the cultures, the formation of ethyldimethylarsine would have been expected.

Challenger and Higginbottom (59), using cultures of S. brevicaulis on glucose-Czapek-Dox medium containing arsenious acid, found that addition of sodium formate or of formaldehyde (free or as various derivatives), with or without formate, had no appreciable influence on the yield of trimethylarsine.

If we assume that selenious and tellurous acids can react in the forms $H \cdot SeO_2OH$ and $H \cdot TeO_2OH$, the formaldehyde hypothesis can similarly be employed to explain their conversion to dimethyl selenide and dimethyl telluride in mould cultures. There is some doubt, however, as to whether selenious acid can react in this form. Strecker and Daniels (198) found that the product from the action of silver selenite on ethyl iodide is identical in boiling point and other physical properties with that obtained from selenium oxychloride ($SeOCl_2$) and sodium ethoxide. They conclude, therefore, that, unlike sulfurous acid, selenious acid or its salts are not capable of tautomerism to the forms $HSeO_2OH$ and $AgSeO_2OAg$. Loevenich, Fromdling, and Fohr have, however, shown that β-naphthylseleninic acid, $C_{10}H_7SeO_2H$, can give rise to the normal ester and also to a selenone (150).

As applied to the fission of disulfides and methylation of the resulting mercaptan, the formaldehyde hypothesis demands the formation of $RSCH_2OH$. Several compounds of this type have been described (148), but they are unstable and easily hydrolyzed. The compound $C_2H_5SCH_2OH$ could not be freed from traces of ethylthiol, and so its capability of reduction to $C_2H_5SCH_3$ in mould cultures could not be determined (64).

Possible origins of formaldehyde

Leaving photosynthesis in green plants out of consideration, we may now consider some possible modes in which formaldehyde might arise and become available as a methylating agent in moulds, animals and, to some extent, in plants.

(1) Deamination of glycine: Schweitzer (188; cited by Robinson (182)) found that potato tyrosinase can oxidize glycine with formation of formaldehyde, carbon dioxide, and ammonia. Similar decompositions of glycine and other amino acids are summarized by Challenger and Higginbottom (59).

Such compounds as choline and betaine, which occur in higher plants, fungi,

and animals, have usually been regarded as arising through methylation of a precursor by formaldehyde or glyoxylic acid resulting (in the case of animals) from the deamination of glycine. It was, in fact, suggested by the author (53) that glycine might by oxidative deamination methylate itself to betaine. On the other hand, du Vigneaud and his colleagues have recently shown in animal experiments that the methyl group of methionine, $CH_3SCH_2CH_2CH(NH_2)COOH$, is concerned in the formation of choline (see page 349) and that the reverse relationship also occurs.

(2) *Oxidative demethylation of* $>NCH_3$ *compounds:* The remarkable experiments of Hess and his coworkers (119–122) established that when formaldehyde reacts with certain primary and secondary alcohols containing a cyclic $>NH$ group (pyrrolidine and piperidine derivatives) this is converted to $>NCH_3$ and the $-CH_2OH$ or $>CHOH$ group is oxidized to $-CHO$ or $=C=O$. Conversely, the resulting *N*-methylated keto acid on treatment with phenylhydrazine or semicarbazide yields a secondary alcohol, the $>NCH_3$ group giving rise to $>NH$ and the phenylhydrazone or semicarbazone of formaldehyde. The reduction of $>NCH_2OH$ to $>NCH_3$ is regarded by Hess as being effected by the $>CHOH$ group and not by excess formaldehyde. Thus, an external secondary alcohol can act as an oxygen acceptor: isopropyl alcohol with formaldehyde and piperidine or diethylamine gives acetone. On the other hand, the conversion of hexahydronicotinic acid to its $>NCH_3$ derivative, formic acid, and carbon dioxide when heated with 2 moles of formaldehyde shows that this can act as an oxygen acceptor in the absence of other suitable substances. See also in this connection (*a*) the absence of carbon dioxide pressure in the sealed tubes used for the interaction of the alkanolamine and formaldehyde, and (*b*) its production when formic acid is also present.

There is much evidence to show that demethylation of methylated amino acids or amines can be effected by animals or animal tissues.

Some interesting results were obtained by Fuchs (96) in a study of the behavior of choline in the body of the dog. Large subcutaneous injections of choline chloride yielded only traces in the urine, indicating considerable breakdown. That this does not take place by way of trimethylamine (as is occasionally the case with microörganisms (174)) is shown by the absence of any abnormal amount of trimethylamine oxide in the urine; trimethylamine normally gives rise to this oxide in animals.

Monomethyl- and dimethyl-aminoethanols, which are allied to choline, also disappear on injection but do not give rise to appreciable amounts of trimethylamine or its oxide. The same is true of methylamine and dimethylamine.

Fuchs concludes that choline and these related compounds undergo demethylation in the dog.[6] For other work leading to similar conclusions see Guggenheim (111).

In this connection the conversion of dimethylaniline to the glycuronate of p-monomethylaminophenol in the rabbit (128) is of interest. Small quantities of monomethylaniline could also be detected in the urine. Demethylation of dimethylaniline is also effected by dogs and o-aminophenol is excreted (129). Lewis and Tager (149) state that N-methyl- and N,N-dimethylsulfanilamides are demethylated when administered to men or mice. (For the recent work on the demethylation of p-dimethylaminoazobenzene in rats and its curative effect on renal hemorrhage in these animals see page 352.)

Bloch and Schoenheimer (30) fed rats with (a) isotopic glycine and (b) isotopic sarcosine (N-methylglycine). Glycine was then isolated from the tissue protein as the trioxalatochromate, the concentration of isotopic nitrogen being almost identical in each case. It is suggested that sarcosine is demethylated in the tissues without loss of nitrogen. This is in agreement with the work of Gordon and Jackson (100) and of Abbott and Lewis (1) on the capacity of sarcosine to replace glycine as a detoxicating agent when benzoic acid is fed to albino rats. On the other hand, N-ethylglycine causes no increase in the rate of excretion of hippuric acid when administered with benzoate to rabbits, suggesting that deëthylation is at any rate a much slower process (2). The oxidative demethylation of sarcosine has now been definitely established in the presence of broken cell preparations of the liver of cats and rabbits, formaldehyde being detected colorimetrically and the resulting glycine determined by van Slyke's method (116). The results with sarcosine are of interest in view of the work of Hess (already cited). The authors point out that other N-methylamino acids are not necessarily metabolized in the same way. Thus Keilin and Hartree (141) found that N-methylalanine gives pyruvic acid and methylamine with amino acid oxidase.

In consequence of the behavior of sarcosine it was to be expected that attempts would be made to discover whether it could act as a methylating agent. Work by du Vigneaud and his colleagues has shown that, unlike certain closely related compounds (which do not eliminate a methyl group as formaldehyde), sarcosine

[6] The possibility does not appear to be excluded that in Fuchs's experiments choline and aminoethanol might disappear through direct conversion to lecithin and cephalin, and that demethylation of choline is not involved. The natural phosphatides probably contain no mono- or di-methylaminoethanol (16, 180, 213; see page 340) and such an explanation leaves the disappearance of these two compounds unexplained.

Preliminary methylation of mono- and di-methylaminoethanols to choline is an obvious explanation, but this is considered improbable by Fuchs because he obtained no betaine in the urine after subcutaneous injection of sarcosine (methylgycine) in a dog. A further alternative explanation of Fuchs's results is that choline might be oxidized to the corresponding aldehyde or to betaine. No search for these compounds in the urine appears to have been made, although Fuchs refers to the work of Mann and Quastel (152a), who observed the conversion of choline to the aldehyde by rat-liver slices.

exerts no methylating action in animal experiments. It can, therefore, be stated that, attractive as is the hypothesis that biological methylation in moulds and animals arises through the agency of formaldehyde produced by deamination of glycine or demethylation of N-methyl compounds, confirmation on the biological side is lacking. There are, however, no grounds for discarding it as a possible mechanism under certain circumstances, although du Vigneaud, by his work on methylation processes in animals, has shown that it cannot be the only one.

(3) *The breakdown of purines through uric acid to glyoxylic acid*: In animal and vegetable tissues there are present enzyme systems which convert nucleic acids to purines (adenine and guanine) and thence by oxidation and deamination to uric acid. Uricase, an enzyme converting uric acid (I) into allantoin (II), occurs in the liver and kidneys of various animals (215) and was found by Nemec (165) in several leguminous plants and by Fosse, Brunel, and de Graeve (91) in higher fungi

Sumi (199) isolated uric acid from the spores of *Aspergillus oryzae*, and Fosse, de Graeve, and Thomas (92) detected it in numerous plants. Allantoin has long been recognized as a product of purine metabolism, and Fosse *et al.* (93, 94) have shown it to be widely distributed in animals and plants, e.g., in *Phaseolus lunatus* and *Acer pseudoplanus*. Fosse and Brunel (90) showed that these two plants, and also others, contain an enzyme *allantoinase*, which hydrolyzes allantoin to allantoic acid (III), which had already been obtained from the same source by Fosse (87, 88).

Brunel (37) has shown that material from many animal and vegetable sources contains an enzyme *allantoicase*, which hydrolyzes allantoic acid to glyoxylic acid and urea (for references to the occurrence of urea in plants, see Brunel's thesis (37)). He then showed that uricase, allantoinase, and allantoicase are all present in the mollusc *Mytilus edulis* (39) and in the mycelium of *Aspergillus niger* when grown on certain media (37, page 134). Uricase was only present when the medium contained uric acid; formation of allantoinase required the presence, among other compounds, of allantoin, whereas allantoicase was formed even when ammonium sulfate was the only source of nitrogen.
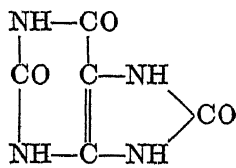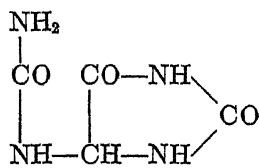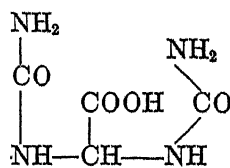
I	II	III
Uric acid	Allantoin	Allantoic acid

The existence of an enzymic system in animals, plants, and at least one mould, capable of producing glyoxylic acid, which is so closely related to formaldehyde, suggested a search for this system in the mycelium of *S. brevicaulis*, although the very special conditions required for its formation by *A. niger* were not a very hopeful sign. Dr. S. Blackburn (29) failed to detect glyoxylic acid in cultures of *S. brevicaulis* grown on glucose-Czapek-Dox medium by the usual sensitive color

reactions, although Dakin (72) mentions its presence in media on which bacteria and moulds have grown. Challenger, Subramaniam, and Walker (65) showed that small amounts of glyoxylic acid are produced by the growth of *A. niger* on citric acid, malonic acid, and acetates (for similar observations, see reference 20).

When the mycelium of *S. brevicaulis*, grown on glucose-Czapek-Dox solution, was incubated for a few hours with allantoin and a few drops of chloroform, no glyoxylic acid could be detected. The mycelium, therefore, does not contain both allantoinase and allantoicase. On similar incubation with allantoin, and boiling the resulting solution with dilute hydrochloric acid, no glyoxylic acid was formed. Hence allantoinase, which produces allantoic acid, was absent, as this acid if formed would have yielded glyoxylic acid on hydrolysis with acid (89, 94). Finally the mycelium was incubated with potassium allantoate; no glyoxylic acid was detected and therefore allantoicase was also absent. A culture of the strain of *S. brevicaulis* used in this work (*Scopulariopsis brevicaulis* (Sacc.) Bainier, in the Baarn *List of Fungi*, 1932) was sent to Dr. Brunel in Paris, who grew the mycelium and confirmed our findings. (The author and Dr. Blackburn are much indebted to him for this coöperation.) There would, therefore, appear to be no evidence for the suggestion that methylation by *S. brevicaulis* is effected by glyoxylic acid arising by the progressive breakdown of uric acid. There remains the somewhat remote possibility that when grown upon arsenical media the mycelium might contain the necessary enzymes, but this has not been investigated. The methylated xanthines, theophylline, theobromine, and caffeine, have often been regarded as waste products of purine metabolism in certain plants, being in this respect analogous to the alkaloids which are, also, frequently highly methylated. To these must now be added 1,3,7,9-tetramethyluric acid, recently separated from the residues accumulated during the isolation of caffeine from tea by Johnson (138).

It is interesting to speculate on the mechanism of these biological methylations in the purine series. There is, of course, no experimental evidence for regarding it as different from that involved in the formation of other natural methyl derivatives. It is, however, clear that the work of Fosse and his colleagues has demonstrated a hitherto unrecognized source of "secondary" formaldehyde in plant metabolism, and it is not impossible that the methylated purines in plants may actually arise by way of glyoxylic acid or formaldehyde originating from nucleic acids through uric acid.

(4) *Assimilation of carbon dioxide:* The possibility that biological methylation may, in some of its aspects, be connected with the utilization of carbon dioxide by animals or moulds would appear worthy of investigation. References are given elsewhere by the author (55).

C. The transfer of a methyl group

The third hypothesis, based on the transfer of a methyl group from some already methylated compound such as choline or betaine, had already been put forward by Riesser (181) to explain the production of creatine in animals and also the formation of alkylated (presumably methylated) derivatives of selenium

and tellurium on administration of compounds of these elements to men and animals (59).

Betaine is of frequent occurrence in plants and has recently been detected in various crustacea (53). It has also been found in yeast, ergot, mushrooms, and in other fungi (112). Betaine is very resistant to attack by many, though not by all, microörganisms and by most animals except ruminants (for references see 118).

Choline, however, is of even more general occurrence in plants and is found combined in almost all organs of men and animals. Its occurrence as acetyl-choline is of great importance in animal physiology. Choline has been isolated from the mycelium of certain moulds (e.g., from A. $sydowi$, where it occurs as the betaine-like sulfate, $(CH_3)\overset{+}{N}_3CH_2CH_2OSO_2\bar{O}$) by Wooley and Peterson (218) and from the pathogenic fungus $Blastomyces$ $dermatiditis$ by Peck and Hauser (170). Moreover, a demethylated derivative of choline, aminoethyl alcohol or cholamine, is found combined in the phosphatide cephalin, and also in the mycelium of $Blastomyces$ $dermatiditis$, although various workers (16, 180, 213) failed to detect mono- or di-methylaminoethanol in the products of the hydrolysis of phosphatides. Simons (193) was unable to detect any demethylation products of choline when S. $brevicaulis$ was grown on a glucose-choline chloride-Czapek-Dox medium with or without arsenious oxide.

Faltis and Holzinger (84) find that dimethylaminoethanol occurs as an ester of cassaic acid in the alkaloid cassaine, obtained from $Erythrophleum$ $guineense$. Blount, Openshaw, and Todd (32) isolated monomethylaminoethanol by hydrolysis of erythrophleine, another alkaloid of the same bean. Here it is combined with erythrophleic acid, which is probably a methoxycassaic acid. Cassaic acid is stated by Faltis and Holzinger to be a hydroxy ketonic acid containing three six-membered rings and one double bond.

Guggenheim (113) discusses two possible origins of aminoethanol in nature: (1) the decarboxylation of serine, $CH_2OHCH(NH_2)COOH$; (2) the condensation of formaldehyde to glycolaldehyde, followed by reaction with ammonia and reduction. It is probable that aminoethanol and choline are interconvertible by way of the methyl derivatives of the former, which is in agreement with the work of du Vigneaud (195) and of Stetten (212).

The origin of Riesser's suggestion regarding the transfer of a methyl group is perhaps to be found in a communication by Hofmeister (127), who, when referring to the formation of methylpyridinium hydroxide and of dimethyl telluride (the formation of the telluride was assumed and not proved) in the animal body stated: "Nach dem Ausgeführten ist anzunehmen dass die CH₃ Gruppen in den Geweben welche das Vermögen der Methylierung besitzen als solche vorgebildt ist. . . . Bei Anwendung von Pyridin und Tellur käme es zur Methylierung dieser während normalerweise methylhaltige Stoffe anderer Art z.B. die Körper der Cholin und der Kreatingruppe entstehen."

Hofmeister does not mention betaine or choline as sources of the methyl group, but only suggests that choline or creatine are the normal products of the methylation process. In support of his views Riesser stated that on heating betaine hydrochloride or choline chloride and sodium formate with sodium

selenite or tellurite, odors resembling those of dimethyl selenide and telluride were produced, but no chemical identification was carried out.

(1) Transfer of methyl groups from betaine

Challenger and Higginbottom (59) and Challenger, Taylor, and Taylor (66) have shown that (a) sodium sulfite, (b) organic disulfides, (c) sodium selenite, and (d) sodium tellurite when heated with betaine (free from hydrochloride, to avoid the formation of methyl chloride) and in the absence of sodium formate yield dimethyl sulfide, methyl alkyl or methyl aryl sulfide, dimethyl selenide, and dimethyl telluride. All these products were identified by the formation of derivatives. The last three reactions (b, c, and d) exhibit a rather close parallel with the behavior of the corresponding compounds in cultures of *S. brevicaulis* (see pages 323, 324, 331). For a reason as yet unexplained the analogous experiment with sodium arsenite gave no trimethylarsine. The suggestion for these experiments was found in the early observation of Willstätter (217) that, on heating, betaine is converted to the methyl ester of dimethylaminoacetic acid, a reaction clearly involving the migration of a methyl group (compare also Straw and Cranfield (197)). It was suggested by Challenger (54) that these pyrogenic reactions proceed somewhat as follows:

$$(1) \quad (CH_3)_3\overset{+}{N}CH_2CO\overset{-}{O} + Na_2SeO_3 = (CH_3)_2NCH_2COONa + CH_3SeO_3Na$$
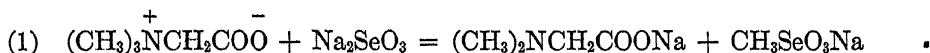
With selenites and tellurites a quaternary salt is probably first formed. The dimethyl selenide presumably arises by decomposition of the sodium methaneselenonate.

$$(2) \quad (CH_3)_3\overset{+}{N}CH_2CO\overset{-}{O} + RSSR = (CH_3)_2NCH_2COOSR + RSCH_3$$
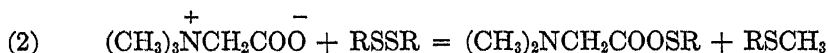
Under similar conditions primary aromatic amines yield *N*-monomethyl derivatives.

Challenger, Taylor, and Taylor (66) then refer to the two mechanisms discussed by Ingold and his collaborators (97, 132–135), who have shown that the reactions

$$(R\overset{+}{N}R'R''R''')\overset{-}{X} \rightarrow RX + NR'R''R''' \quad \text{and} \quad (R\overset{+}{S}R'R'')\overset{-}{X} = RX + R'SR''$$
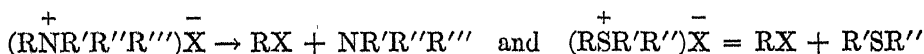
may be unimolecular or bimolecular according to the polar character of R and X. The unimolecular reaction proceeds by the separation of an ion R^+, which then unites with X^-, but in the bimolecular reaction no free ion is eliminated. The authors then state that "in the absence of any evidence as to the kinetics of the various betaine decompositions—they occur at high temperatures—it is impossible to say whether a free methyl ion is concerned in the reactions."

Experimental evidence is equally lacking as regards the kinetics of the production of methyl derivatives by living cells. Considering first a unimolecular mechanism as given above (Type S_N1, Hughes and Ingold (133), Gleave, Hughes, and Ingold (97)), it was first pointed out by Challenger (54) that almost all the compounds which have been found to undergo methylation by

moulds or on introduction into the animal body are capable of furnishing negative ions, e.g., sodium arsenite, selenite, and tellurite, alkylthiols (arising from dialkyl disulfides) and also nicotinic acid, which gives trigonelline (5, 130). Moreover, all these compounds contain unshared electrons, so that coördination of a positive methyl group by the ion would lead to the formation of a neutral molecule which could then undergo reduction and ionization, followed by further coördination of a CH_3^+ radical. The positive methyl group may be assumed to be derived from either betaine, choline, or methionine, leaving in either case a negative ion which would compensate the hydrogen ion of the compound RH undergoing methylation (66):

$$(CH_3)_3\overset{+}{N}CH_2CO\overset{-}{O} + RH = (CH_3)_2NCH_2COOH + RCH_3$$

$$\underbrace{(CH_3)_3\overset{+}{N}CH_2CH_2OH}_{OH^-} + RH = (CH_3)_2NCH_2CH_2OH\cdot + RCH_3 + HOH$$
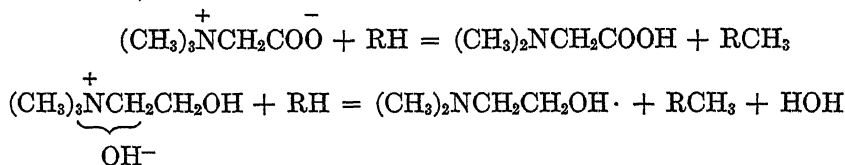
(2) Methylation of arsenic, selenium, and tellurium compounds

The process suggested by the Leeds School may be illustrated in the case of arsenious and selenious acids:

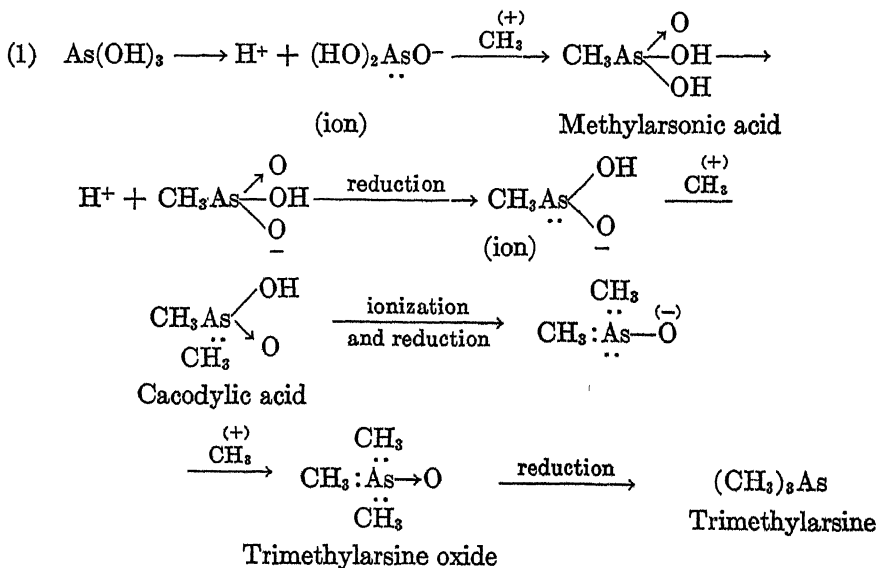(1) $As(OH)_3 \longrightarrow H^+ + (HO)_2As\overset{..}{O}^- \xrightarrow{\overset{(+)}{CH_3}} CH_3As\overset{O}{\underset{OH}{\diagdown}}{}_{OH} \longrightarrow$

                (ion)   Methylarsonic acid

$H^+ + CH_3As{\overset{O}{\underset{O^-}{\diagdown}}}_{OH} \xrightarrow{\text{reduction}} CH_3A\overset{..}{s}{\overset{OH}{\underset{O^-}{\diagdown}}} \quad \overset{(+)}{CH_3}$

                           (ion)

$CH_3As{\overset{OH}{\underset{\overset{..}{CH_3}}{\diagdown}}}_O \xrightarrow[\text{and reduction}]{\text{ionization}} CH_3:\overset{\overset{CH_3}{..}}{As}{-}\overset{(-)}{O}$

Cacodylic acid

$\xrightarrow{\overset{(+)}{CH_3}} CH_3:\overset{\overset{CH_3}{..}}{\underset{CH_3}{As}}{\to}O \xrightarrow{\text{reduction}} (CH_3)_3As$

                                              Trimethylarsine

Trimethylarsine oxide

None of the suggested intermediate compounds have been detected in mould cultures, but methylarsonic acid, cacodylic acid, and hydroxytrimethylarsonium nitrate (the nitrate of trimethylarsine oxide) all yield trimethylarsine when present as substrates in bread cultures of *S. brevicaulis* (61). Furthermore, it has been shown earlier in this review that alkyl- and dialkyl-arsonic acids, $RAsO(OH)_2$ and R_2AsOOH (where R may be ethyl, *n*-propyl, or allyl), similarly

yield mixed arsines, $RAs(CH_3)_2$ and R_2AsCH_3. Ethylmethyl-n-propylarsine was obtained in this manner from ethyl-n-propylarsonic acid (58, 63; see page 322).

$$(2) \quad H_2SeO_3 \longrightarrow H^+ + \underset{\text{(ion)}}{:Se\overset{\overset{(-)}{O}}{\underset{O}{\diagdown}}OH} \xrightarrow{\overset{(+)}{CH_3}} \underset{\text{Methaneselenonic acid}}{CH_3Se\overset{\overset{O}{\diagup}}{\underset{O}{\diagdown}}OH}$$

$$\xrightarrow[\text{and reduction}]{\text{ionization}} \underset{\substack{\text{Ion of methanesele-}\\ \text{ninic acid}}}{CH_3Se\overset{\overset{\bar{O}}{\diagup}}{\underset{O}{\diagdown}}:} \xrightarrow{\overset{(+)}{CH_3}} \underset{\substack{\text{Dimethyl}\\ \text{selenone}}}{(CH_3)_2Se\overset{\overset{O}{\diagup}}{\underset{O}{\diagdown}}} \xrightarrow{\text{reduction}} \underset{\substack{\text{Dimethyl}\\ \text{selenide}}}{(CH_3)_2\ddot{Se}:}$$
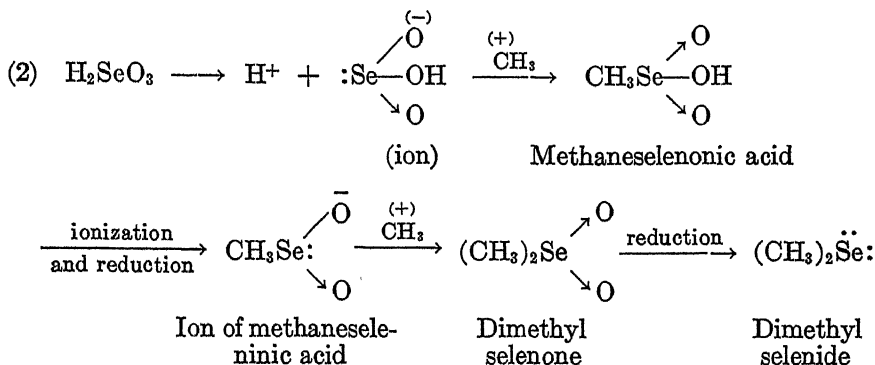
A similar series of reactions would explain the formation of dimethyl telluride from salts of tellurous acid.

It will be seen that on this view of the mechanism the postulated intermediate products are also required by the formaldehyde hypothesis, which, however, demands the prior formation of a hydroxymethyl group at each stage of the methylation. None of the three postulated intermediate selenium compounds have been detected in the culture media. Dimethyl selenone has not been prepared. For experimental work designed to test the possibility of this scheme, see Bird and Challenger (25a), who have shown that bread cultures of *S. brevicaulis* and certain *Penicillia* convert methane-, ethane-, and propane-1-seleninic acids, $RSeO_2H$, to dimethyl-, ethyl methyl, and methyl n-propyl selenides, $RSeCH_3$, as required by the mechanism outlined above. The authors point out, however, that the simultaneous production of traces of alkylselenothiols, $RSeH$, or of dialkyl diselenides introduces some ambiguity into the interpretation of these results since, by analogy with the behavior of alkylthiols and disulfides in cultures of *S. brevicaulis* (see below) either type of compound might be converted to a methyl alkyl selenide without passing through the selenone, CH_3SeO_2R. Neglecting this possibility, which the authors regard as somewhat improbable, the formation of methyl alkyl selenide may be represented thus:

$$\overset{-}{RSeO_2} + \overset{+}{CH_3} \rightarrow RSeO_2CH_3 \rightarrow RSeCH_3$$
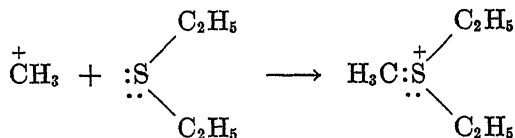
Bird and Challenger also examined the behavior of the potassium salts of methane-, ethane-, and propane-1-selenonic acids, $RSeO_2OK$, in cultures of the same moulds with a rather surprising result, only dimethyl selenide being formed in each case. This is presumably due to breakdown of the selenonate in the cultures, giving ROH and $KHSeO_3$. This reaction takes place in the test-tube on warming with dilute acid or alkali. This observation is not regarded as vitiating the suggested mechanism, since it is possible that the methaneselenonic acid postulated as the first intermediate product might be sufficiently stable, when formed within the cell, to pass on to the next stage without hydrolysis.
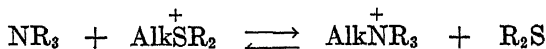
(3) Methylation of sulfur compounds

Work carried out with Blackburn and with Rawlings (56, 63) suggests that the methyl alkyl sulfides obtained by addition of dialkyl disulfides to cultures of *S. brevicaulis* arise by methylation of an alkylthiol first produced. Ionization of this, followed by coördination of CH_3, would explain the observed facts:

$$RSH \rightarrow \overset{-}{R}S + \overset{+}{H} \tag{1}$$

$$\overset{-}{R}S + \overset{+}{C}H_3 \rightarrow RSCH_3 \tag{2}$$

Alternatively, coördination of the methyl ion by the disulfide may occur prior to fission (66). Neuberg and Grosser (167) state that diethylmethylsulfonium hydroxide is a normal ingredient of a dog's urine, yielding diethyl sulfide on warming with alkali. They also state that diethyl sulfide on administration to dogs is converted to the methylsulfonium base. This can be expressed thus:

$$\overset{+}{C}H_3 + :S \begin{matrix} C_2H_5 \\ \diagup \\ \diagdown \\ C_2H_5 \end{matrix} \longrightarrow H_3C:\overset{+}{S} \begin{matrix} C_2H_5 \\ \diagup \\ \diagdown \\ C_2H_5 \end{matrix}$$

and represents a reversal of the reaction

$$NR_3 + Alk\overset{+}{S}R_2 \rightleftharpoons Alk\overset{+}{N}R_3 + R_2S$$

envisaged by Hughes and Ingold (134), who remark that instances of this reaction have not been recorded. Attempts by B. Taylor (201) to detect the formation of this sulfonium base on addition of diethyl sulfide to cultures of *S. brevicaulis* on glucose-Czapek-Dox medium failed.

Addition of aqueous hydrogen sulfide, or of sodium sulfide, thiosulfate, tetrathionate, sulfite, or methanesulfonate to cultures of the mould failed to give any dimethyl sulfide. Sodium ethanesulfinate, $C_2H_5SO_2Na$, gave no ethyl methyl sulfide. The apparent inertness of the last three compounds, both in bread and in liquid cultures, was at first somewhat surprising, in view of the ready reactivity of sodium selenite and sodium alkylseleninate. It appeared possible that this failure might be ascribed to the formation of methanesulfonic acid or of dimethyl sulfone by reactions analogous to those postulated in the case of sodium selenite.

Diethyl sulfone, unlike diethyl sulfoxide (62), is not reduced to diethyl sulfide in bread cultures of *S. brevicaulis*, and sulfones, if formed, would probably accumulate. (This difference may be compared with the difference in the case of the chemical reduction of sulfites and sulfates to hydrogen sulfide.) Careful extraction of the liquid culture media containing sodium sulfite, methanesulfonate, or ethanesulfinate with chloroform gave no dimethyl or ethyl methyl sulfone. Methanesulfonic acid, also containing the stable $>SO_2$ group, might also be expected to resist further reaction, in which case neither sulfone nor

sulfide would be formed. Attempts to detect this acid in liquid cultures containing sodium sulfite failed, although several attempts were made. The detection of small quantities of alkylsulfonic acids is, however, very troublesome. These experiments were carried out by Dr. Bird and Mr. J. W. Fletcher.

Even on the assumption that sodium methanesulfonate escaped detection in the sulfite cultures, it is difficult to explain the non-formation of ethyl methyl sulfone from sodium ethanesulfinate.

(4) Methylation of nitrogen compounds

Coördination of a positive methyl ion would also explain the well-known conversion of pyridine and quinoline to methylpyridinium and methylquinolinium hydroxides in the body of the dog (126, 145, 200).

The formation of trigonelline or of N'-methylnicotinamide (see below) on administration of nicotinic acid to various animals may be explained in the same way.
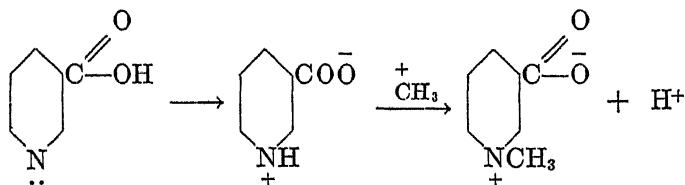
This mechanism is in agreement with the twin-ion structure for betaines such as nicotinic acid and trigonelline. The hydrogen ion of the nicotinic acid yields RH, as before.

Ackerman (5) showed that this formation of trigonelline in the dog is accompanied by that of nicotinuric acid (see also 130, 131)

and in previous communications by the author (53, 59) this has been cited in support of the view that glycine (with or without previous oxidative deamination to formaldehyde) is concerned in both changes. It should be pointed out that the formation of nicotinuric acid is not incompatible with the view that the methyl group of trigonelline is derived from choline, betaine, or some similar substance. Complete demethylation of the first two compounds would lead to aminoethyl alcohol ($NH_2CH_2CH_2OH$) and to glycine (NH_2CH_2COOH) either of which, assuming preliminary oxidation in the first case, could yield nicotinuric acid.

Further work by Najjar et al. (161, 162, 163) and by Huff and Perlzweig (130, 131) indicates that in man and in rats doses of either nicotinic acid or its amide result in the excretion of N'-methylnicotinamide as the chief end product

rather than trigonelline. After large doses of nicotinic acid to rats, however, there appears in the urine a considerable fraction of the total methylated product which is not the amide.

Perlzweig, Bernheim, and Bernheim (171) have shown that nicotinamide when incubated with rat liver slices at 37°C. is converted into its N'-methyl derivative. The process is strictly aerobic, and requires unbroken cells; minced liver even in the presence of oxygen is inert. Nicotinic acid is not methylated under these conditions, nor is the amide methylated by rat kidney or muscle. The necessity for an intact cell recalls the results of Challenger and Higginbottom (59), who were unable to observe the formation of trimethylarsine from arsenious acid and various sterile preparations obtained from cultures of *S. brevicaulis* e.g., by submitting the mycelium to great pressure, thus obtaining a "press juice," by treating the mycelium with acetone, or by filtering the culture medium through porcelain.

Maassen (152) states that a press juice obtained from the mycelium of *S. brevicaulis* or the mycelium itself, after killing with alcohol, chloroform, or ether, gave no odor with sodium tellurite. Smith and Cameron (194) also failed to obtain an active enzyme preparation.

Hofmeister (127) and Maassen (152) showed that whereas the intact, minced, or crushed tissue of the liver of dogs and especially the lungs and testicles of dogs and the testicles of fishes readily convert inorganic compounds of selenium and tellurium into odorous substances, presumably dimethyl selenide and dimethyl telluride, attempts to obtain an active press juice from the organs failed. Exposure of the tissues to low temperatures had no harmful effect on the activity, but heating at 40–50°C. or treatment with acids, alkalis, concentrated salt solutions, or alcohol destroyed it at once. The methylating process is therefore presumably enzymic, but owing to their failure to obtain active preparations after separation from the tissue both Maassen and Hofmeister concluded that it was definitely bound up with the life of the cell.

In their experiments with an entirely different substance—nicotinamide— Perlzweig *et al.* (171) observed no methylation using minced liver. Further work under strictly comparable conditions will be necessary before the effect of destruction of the cell structure on biological methylation in animals can be satisfactorily assessed.

As already stated (see page 341), the transfer of a methyl group might take place by a bimolecular mechanism of Ingold's S_N2 type. Hughes and Ingold (134), when discussing the kinetics of the reaction between alkyl halides and sodium thiosulfate or ethyl sodioacetoacetate, state, ". . . mechanism S_N1 if present would not normally be observed, the carbon cation produced by a primary ionization would react much more often with the solvent than with the ionic reagent, and the result would be a hydrolysis or alcoholysis." From this it would appear that, as biological processes occur in an aqueous medium, the participation of a positive methyl ion would involve the simultaneous if not preponderating production of methyl alcohol.

Raistrick (177), in an investigation of the carbon balance sheet of three

different strains of *S. brevicaulis* grown on aqueous glucose and inorganic (Czapek-Dox) salts, found no metabolic products other than carbon dioxide. One strain of *Penicillium chrysogenum* and one of *P. notatum* were shown by Bird and Challenger (25) to produce dimethyl selenide and dimethyl telluride in bread cultures containing selenite or tellurite. Raistrick *et al.* (178) record that three species of *P. chrysogenum* and one of *P. notatum* do not form alcohol when grown on glucose-Czapek-Dox solution, except in very small amounts, although they produce other non-volatile metabolic products. The term "alcohol" refers, of course, to ethyl alcohol, but methyl alcohol would not have escaped detection.

It is not possible to state whether the strains of *P. chrysogenum* and *P. notatum* used by Bird and Challenger were identical with any of those cited by Raistrick and it should be mentioned that (178a) some species of *Aspergillus nidulans* produce alcohol, whereas others do not. An examination by Dr. Higginbottom of cultures of *S. brevicaulis* on the same medium (200, 200, and 1000 cc. were separately distilled and the "first runnings" tested with acidified potassium dichromate) failed to reveal the presence of any methyl alcohol. As it seemed possible that the methylation processes of the mould might only function in presence of a poison, one culture (200 cc.) containing arsenious acid was also examined with, however, a negative result.

There is at present, therefore, no evidence for the production of methyl alcohol by *S. brevicaulis*. Further experiments with larger quantities are in progress.

The alternative to methylation by elimination of a positive methyl ion is a bimolecular reaction of the S_N2 type (97, 133), which they express thus:

$$R'R''R'''N - R\}X \rightarrow NR'R''R''' + RX$$
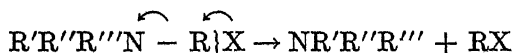
Here X would represent the arsenite, tellurite, etc., ion. This differs from the S_N1 reaction only in its kinetics and not in its products. If, as seems probable for the reasons just stated, this bimolecular mechanism would appear preferable, then the representation of the coördination of CH_3^+ by the arsenite or other negative ion should be replaced by a scheme in which the transfer of methyl takes place without actual separation as an ion. Since, however, this also ultimately involves the attachment of methyl to the unshared electrons of the metalloid, the formulations on pages 342 and 343 may be retained for convenience in representing the suggested intermediate stages in the methylation process.
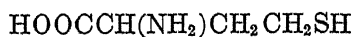
(5) Transmethylation: du Vigneaud's experiments using isotopic indicators

The suggestion that certain biological methylations in animals might be conditioned by choline or betaine, first outlined by Riesser (181), was amplified by Challenger and Higginbottom (59) and expanded to include the similar reactions exhibited by *S. brevicaulis* and certain other moulds. These authors stated, "...it is not impossible that some ingredient of the cell substance containing a methylated nitrogen atom may, under the special circumstances obtaining in the cell, lose a methyl group which, if it be eliminated with a positive charge, could
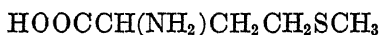
be easily coördinated by the unshared electrons of tervalent arsenic or of quadrivalent selenium or tellurium." This suggestion, now further developed in this communication (the sections dealing with the coördination of a methyl ion have been in typescript since June, 1939), receives support from the recent work of du Vigneaud and his colleagues. They have shown (67, 209, 210) that homocystine (IV) (after conversion to homocysteine (V) can replace methionine (VI) in the diet of the white rat only in the presence of choline and certain related substances such as betaine, which, however, produces the effect more slowly than choline. The authors suggested that a methyl group is transferred from the nitrogen of choline or betaine to the sulfur of homocysteine to give methionine and considered that the reaction might be reversible, methionine acting as a donor of methyl groups to a choline precursor.[7]
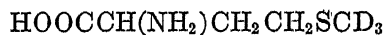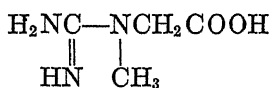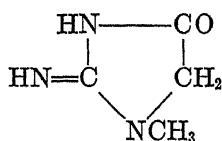
$$(HOOCCH(NH_2)CH_2CH_2S)_2$$

IV

Homocystine

$$HOOCCH(NH_2)CH_2CH_2SH$$

V

Homocysteine

$$HOOCCH(NH_2)CH_2CH_2SCH_3$$

VI

Methionine

$$HOOCCH(NH_2)CH_2CH_2SCD_3$$

VII

Deuteriomethionine

$$H_2NC-NCH_2COOH$$
$$\overset{\|}{HN} \quad \overset{|}{CH_3}$$

VIII

Creatine

$$HN-CO$$
$$HN=C \quad CH_2$$
$$NCH_3$$

IX

Creatinine

It will be seen later (page 352) that choline prevents a pathological condition known as "fatty infiltration" of the liver in rats. It appeared possible, though rather improbable, that the growth observed in the dietary experiments just outlined might have been simply due to this particular effect of choline, the liver thus being enabled to remain healthy and to carry out methylation by some other means than a transference of methyl from choline.

This explanation was, however, disproved when the choline was replaced by its ethyl analogue,

$$(C_2H_5)_3NCH_2CH_2OH$$
$$OH$$
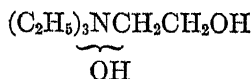
which can also prevent fatty infiltration. This compound did not allow of the growth of rats maintained on a choline-methionine-free diet containing homocystine. du Vigneaud points out (208) that had an ethyl group been transferred, ethionine (S-ethylhomocysteine, $C_2H_5SCH_2CH_2CH(NH_2)COOH$) would have been formed and this was shown by Dyer (79) to be incapable of replacing

[7] Professor du Vigneaud very kindly informed the authors of these early experiments in April, 1939.

methionine in the diet. du Vigneaud also showed that on feeding ethionine and choline on a methionine-free diet to rats no growth resulted, indicating that homocysteine is nôt formed from ethionine in the body. This stability of the —SC_2H_5 link in ethionine recalls the difficulty experienced in deëthylating ethylglycine in rabbits (see page 348) or certain N-ethylphenazine derivatives under purely chemical conditions (154a).

du Vigneaud's "transmethylation" hypothesis, based on his dietary experiments with white rats, was tested by the use of specimens of deuteriomethionine (VII) containing (a) 83.6 and (b) 87.5 atom per cent of deuterium in the methyl group. These were fed to rats kept on a methionine-choline-free diet (211). Earlier work had shown that the deuterium content of the urinary creatinine (IX) closely follows that of the creatine (VIII) and choline of the tissues. The experiment with specimen (a) was, therefore, continued for 94 days until the methyl group of the creatinine contained 72.4 atom per cent. The animal was then killed and the choline isolated from the tissues as the chloroplatinate. The atom percentage of deuterium in the methyl groups of this choline was found to be 74.2, the corresponding figure for the tissue creatine being 73. These figures represent in all three cases approximately 85 per cent of the theoretically possible amount of deuterium, assuming that all the methyl groups had come from the deuteriomethionine. This figure is the "deuterium ratio," i.e., atom per cent deuterium in methyl group of isolated compound per atom per cent deuterium in methyl group of deuteriomethionine administered $\times 100$. For other results with specimens (a) and (b) the original paper must be consulted. By oxidation of the choline to trimethylamine with potassium permanganate and analysis of the hydrochloride it was shown that the whole of the deuterium was contained in the methyl groups.

du Vigneaud and his colleagues conclude that these reactions are true transmethylations (the methyl group being transferred as a whole) and that they do not involve the elimination of dideuterioformaldehyde, CD_2O. On the formaldehyde theory of methylation dideuterioformaldehyde, if produced, would react with the amino group of the choline precursor, presumably ethanolamine, $HOCH_2CH_2NH_2$ (see 195), to give —$NHCD_2OH$, which on reduction in the organism would give —$NHCD_2H$ and not —$NHCD_3$. It would then follow that the deuterium content of the methyl groups of the choline could not rise above two-thirds of the concentration of the deuterium in the methyl group of the methionine administered, i.e., the "deuterium ratio" would have a maximum of 66.6 per cent. Similar arguments hold for the deuteriocreatine.

du Vigneaud et al. (212) then administered trideuteriocholine

$$(CD_3)_3 \overset{+}{N} CH_2 CH_2 OH$$
$$\underbrace{\hspace{3cm}}$$
$$OH$$
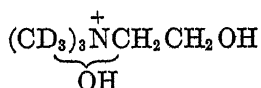
to rats maintained on a methionine-choline-free diet containing homocystine for 23 and 56 days, respectively. On isolation of the creatine from the body tissues the deuterium content of the two samples was 24 per cent and 29 per cent

of the theoretical maximum, thus proving that the methyl groups of choline can also take part in transmethylation. This transfer also takes place, though to a lesser extent, when no homocystine is given or when ordinary methionine is given instead of homocystine.

The most interesting result obtained by du Vigneaud in this particular investigation is, however, the demonstration of the transfer of methyl from choline, giving rise to methionine by the detection of the deuteriomethyl group in tissue methionine. Furthermore this transmethylation was shown to occur when deuteriocholine was administered without homocystine in the diet and even when ordinary methionine was given along with deuteriocholine.

The authors consider that homocysteine is formed during the catabolism of methionine by the animal, thus enabling methionine to be re-formed by means of the methyl group supplied by choline. Continuous synthesis of methionine therefore occurs, although more than enough methionine is supplied in the diet. Similarly, experiments in which deuteriomethionine and ordinary choline were fed together show that the formation of choline from methionine proceeds even with an adequate supply of choline.

The determination of the deuteriomethionine was carried out by fission of the —SCD_3 group by heating with hydriodic acid. The methyl iodide (CD_3I) thus formed was absorbed in alcoholic trimethylamine cooled with solid carbon dioxide. The resulting tetramethylammonium iodide was converted to the chloride with silver chloride and the percentage of deuterium determined in the corresponding chloroplatinate.
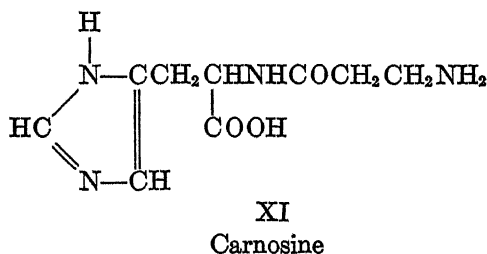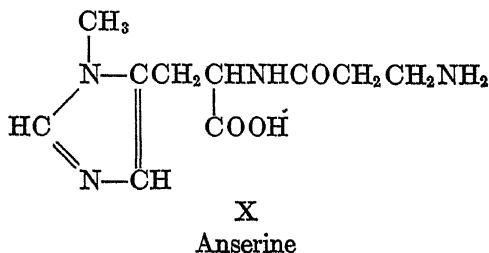
Control experiments showed that some loss, i.e., exchange, of deuterium occurs due to fission of the C—D_3 linkage by the hydriodic acid. Thus the tetramethylammonium iodide so obtained contained 66–72 per cent of the calculated amount of deuterium. The values obtained for the isotopic content of tissue methionine are therefore minimal figures.

Deuterium–hydrogen exchange also occurs when deuteriomethionine is heated with aqueous 20 per cent sodium hydroxide for 23 hr. On the other hand, the C—D bond in the N—CD_3 group of deuteriocholine is not labilized by boiling normal hydrochloric acid, boiling 5 per cent barium hydroxide, or hot alkaline potassium permanganate solutions.

Further experimental work by du Vigneaud and his colleagues (186a) has established the occurrence of transmethylation in another animal, the rabbit. Deuteriomethionine (79 atom per cent D in the methyl group) was administered to the extent of 0.5 per cent of the diet for 8 days and 1.0 per cent for a further 20 days. At the end of that time the creatinine of the urine, the free (water-soluble) and bound (ether-soluble) choline of the tissues, and the anserine (X) of the muscle were analyzed, the deuterium ratios being 21.4, 9.2, 4.9, and 1.9, respectively. The basal diet contained fibrin and hence some ordinary methionine was present. Consequently the above ratios are minimal values. The anserine was separated by alternate formation of the mercury and copper derivatives and analyzed as the copper compound. Choline and creatinine were analyzed as the chloroplatinate and double potassium picrate, respectively.

The rate of transfer of methyl from methionine giving anserine is much slower than the analogous process which yields creatinine.

The authors point out that although rabbit muscle contains both carnosine (XI) and anserine, the latter compound greatly predominates.

$$CH_3$$
$$N—CCH_2 CHNHCOCH_2 CH_2 NH_2$$
$$HC \qquad \qquad COOH$$
$$N—CH$$

X

Anserine

$$H$$
$$N—CCH_2 CHNHCOCH_2 CH_2 NH_2$$
$$HC \qquad \qquad COOH$$
$$N—CH$$

XI

Carnosine

A further advance was marked by the recent announcement of Simmonds and du Vigneaud (191) that, using the isotope technique, they had shown that the methyl group of dietary methionine can be used by man in the synthesis of choline and creatinine. A healthy adult male ingested 6 g. of trideuteriomethionine (73.3 atom per cent D in the methyl group) during 3 days. After 72 hr. the deuterium ratio was 0.54 ± 0.06 in the case of the creatinine zinc chloride compound of the urine and 1.9 ± 0.1 for the choline chloroplatinate obtained from 350 cc. of the blood. These low figures are due, of course, to the short duration of the experiment.

(6) Transmethylation in wheat germs

Barrenscheen and Valyi-Nagy (14a) have recently shown that methionine increases the creatine synthesis from glycocyamine (guanidinoacetic acid) by wheat germs, six to eight fold. The process is obligatory aerobic, the sulfur of the methionine being oxidized to sulfate, corresponding to 25 per cent of the transformed methionine. Plant tissues transform glycine in presence of methionine to betaine. Here again oxidation of the methionine occurs.

XI. LABILE METHYL GROUPS IN RELATION TO OTHER BIOLOGICAL PROCESSES

The work of du Vigneaud and his colleagues has clearly established that choline is concerned with methylation in white rats by virtue of its capacity to transfer its methyl groups.

Two pathological conditions have been extensively studied in rats: namely, fatty livers and hemorrhagic kidneys. These conditions can be produced on a

diet deficient in choline.   A valuable summary of work in this field is given by
McHenry (154) and Griffith (106; this reference also contains an account by du
Vigneaud (208) of much of his recent work on transmethylation).

McHenry states that a marked increase in liver fat can be noted within a day
after rats are placed on a choline-free diet and the renal hemorrhages are well
marked within 10 days.   Both these effects can be cured by administration of
choline, methionine, or betaine with the diet; by analogy with du Vigneaud's
work this suggests that labile methyl groups may be concerned.   The curative
action on fatty livers is known as a lipotropic effect.

McHenry summarizes the possible modes of action of choline in the animal
body as (1) stimulation of the formation of phospholipoids, (2) formation of
acetylcholine, (3) transmethylation.   Both in the case of fatty livers and hemor-
rhagic kidneys he is inclined to ascribe the curative action of choline to the first
mode of action rather than to the third, and cites the established case of the
lipotropic action of the ethyl analogue of choline

$$(CH_3CH_2)_3\overset{+}{N}CH_2CH_2OH$$
$$\underbrace{}_{OH^-}$$
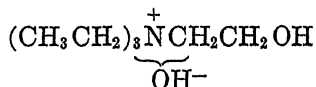
as showing that labile methyl is not an essential requirement for this effect.
(This triethylammonium base cannot, however, replace choline in du Vigneaud's
experiments on the utilization of homocystine by white rats.)

Griffith (106) states that it seems probable that the choline phospholipoids
are involved in the problem of the formation (and spontaneous cure) of the renal
lesions, but that the whole picture may be complicated by variations in the
dietary or metabolic supply of compounds containing labile methyl groups or of
other substances.

It appears impossible at present to decide on the mechanism by which fatty
livers and the kidney lesions are cured by choline, betaine, and methionine—
and hemorrhagic kidneys by p-dimethylaminoazobenzene—but it seems probable
that labile methyl groups play a part in many if not all of the effects.   There is
no doubt that in recent years the methyl group has acquired a greatly enhanced
importance in biochemistry.

Griffith and Mulford (107) in quantitative experiments have compared the
choline-like activity of methionine and betaine with respect to fatty livers and
kidney lesions in rats and find that "the methyl of methionine is efficiently
utilised whereas betaine has but one-third the protective action of choline, as if
only one of its methyl groups is used in the synthesis of choline."

This recalls the observation of du Vigneaud that as a source of labile methyl
for converting homocystine to methionine and so promoting the growth of white
rats, betaine is inferior to choline.   Aminoethanol and its monomethyl and
dimethyl compounds all occur in nature, and the complete transfer of methyl
from choline may be possible.   It will be recalled that Willstätter and his
colleagues (66, 217) showed that betaine is converted by heat to the methyl

ester of dimethylaminoacetic acid, owing to the transfer of one methyl group. Of course, *in vivo*, further demethylation may occur giving finally the methyl ester of glycine—possibly by transmethylation, possibly by oxidative demethylation. Evidence on this point is lacking. It is, however, interesting to speculate as to whether one or three of the methyl groups of betaine are available for transmethylation. Here it should be recalled (see page 337) that sarcosine or methylglycine, CH_3NHCH_2COOH, is stated to lose a methyl group as formaldehyde in the presence of kidney slices (116) but is incapable of participating in transmethylation under the conditions employed by du Vigneaud.

Griffith and Mulford (107) find that nicotinic acid has an opposite effect to that of choline on the incidence and severity of renal lesions or the deposition of liver fat, "possibly because of the diversion of some labile methyl for the formation of trigonelline" (5, 130). It would be useful to determine whether a similar antagonism could be demonstrated between choline and such compounds as pyridine, quinoline, dialkyl disulfides, selenites, tellurites, and glycocyamine, all of which are well-recognized as methyl acceptors in animals or moulds.

Another compound which is antagonistic to choline as regards the lipotropic effect in rats is cystine. The effect is not, however, proportional to the amount of cystine fed and is regarded by Griffith (106) as "not directly related to the metabolism of choline but due to a stimulation of metabolism which is the result of a supplement of cystine in a cystine-deficient diet."

The effect of *S*-methylcysteine,

$$CH_3SCH_2CH(NH_2)COOH$$
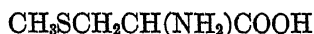
on the production or cure of fatty livers does not seem to have been investigated. Should this compound prove to have a lipotropic action as has methionine, further examination of the cystine effect might be worth while.

The "diversion of some labile methyl", which Griffith and Mulford regard as possibly accelerating the production of fatty livers and the kidney lesions already discussed, may also play an indirect part in facilitating the formation of liver tumors in rats receiving 2-acetylaminofluorene. Bielschowsky (23) finds that 2-acetylaminofluorene is carcinogenic for white rats; 4 mg. per rat and day added to the standard diet for 20–30 weeks produces malignant tumors in different organs. In female rats the majority of these tumors are adenocarcinomas of the breast evident on the average after 250 days. Addition of 20 mg. of glycocyamine per rat and day to the acetylaminofluorene diet accelerates the appearance of breast tumors and at the same time increases considerably the number of liver tumors in female rats. The results suggest that the reduction of available labile methyl groups by the conversion of glycocyamine into creatine enhances the carcinogenic action of 2-acetylaminofluorene.

The full details of this work have not yet been published, but it appears possible that the reduction of available methyl groups may facilitate the formation of fatty livers and later of cirrhotic livers. There is evidence for believing that these conditions are frequently preliminaries to the formation of liver

tumors. Here again it would be interesting to study the effect of other methyl acceptors.

2-Acetylaminofluorene   Glycocyamine   Creatine
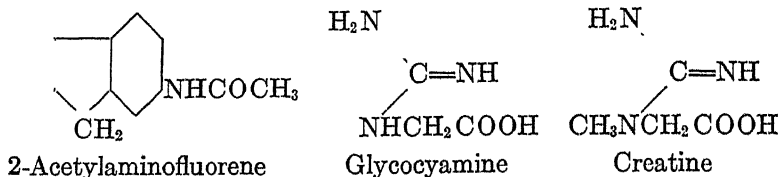
In this connection it may be mentioned that Nelson, Fitzhugh, and Calvery (164) have shown that liver tumors following cirrhosis can be produced in rats by a diet containing selenium at levels of 5, 7, and 10 parts per million. The selenium was administered either as a mixture of potassium ammonium sulfide and selenide, containing 48 g. of selenium per liter, or in the form of seleniferous grain containing sulfur and selenium in organic combination, probably as an amino acid or amino acids of the sulfide type. Tumors were not observed earlier than 18 months but many occurred at 24 months. (Liver damage in rats fed on seleniferous cereals was first observed by Franke (95).)

The authors make no reference to a possible "side-tracking" or "diversion" of labile methyl with subsequent liver damage in these selenium experiments, but selenites, selenates, and alkylseleninic acids, $C_nH_{2n+1}SeO_2H$, are methyl acceptors (25a, 62) in mould cultures and the first two classes of compound doubtless in the animal body also (see 25, 62). The effect of inorganic selenides in mould cultures has not been studied, but the negative selenide ion with its unshared electrons should readily give rise to dimethyl selenide. Apart from this probability the partial oxidation of inorganic selenides to selenites or selenates might be expected and this would probably also be true of selenium in amino acid combination since the sulfur of methionine is converted to sulfate in the body.

At this early stage in the development of these studies of new carcinogenic agents too much stress must not be laid on analogies, but the fact that on certain diets nicotinic acid is antagonistic to the lipotropic effect of choline and that selenium and glycocyamine are concerned directly or indirectly with tumor formation should certainly be noted, these three agents being methyl acceptors.

This survey may conveniently close with a short account of some aspects of a subject which is at present attracting much attention—the carcinogenic action of derivatives of azobenzene. Four such compounds have been found to produce this effect in mice (146a).
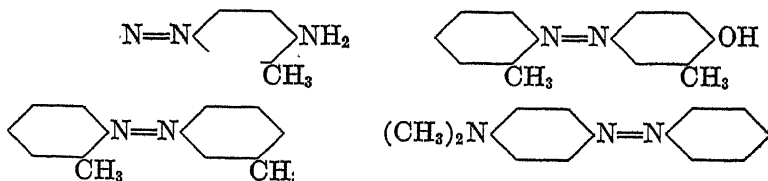
Among these the most important is *p*-dimethylaminoazobenzene, which produces liver tumors when fed to rats, an effect first observed by Kinosita and recently

discussed from the chemical standpoint by Cook (69). Kinosita found that p-aminoazobenzene is not carcinogenic (142). Diets high in protein and vitamin B markedly reduce the carcinogenicity of p-dimethylaminoazobenzene, and the question arose whether these ingredients of the diet act by causing demethylation (136a).

Stevenson, Dobriner, and Rhoads (196) found that in rats demethylation does occur accompanied by fission and reduction of the azo linkage, and that the urine contains p-aminophenol, N-acetyl-p-aminophenol, p-phenylenediamine, and N,N'-diacetyl-p-phenylenediamine. The acetylation is presumably a detoxication and is frequently observed on administration of aromatic amines. This behavior recalls the demethylation of monomethyl- and dimethyl-anilines in the rabbit (128, 129). For the behavior of other N-methylated aromatic amines in animals see Hildebrandt (124).

XII. CONCLUSION

When discussing transmethylation, du Vigneaud et al. (211) state, "... we do not know whether methionine and choline act directly or whether they are precursors of derivatives from which the methyl groups are released. . . . The ability of choline to give up methyl groups in the metabolic process is . . . puzzling in view of the stability of the bond between methyl . . . and nitrogen in choline in ordinary in vitro reactions." This stability is contrasted with "the well-known conversion of betaine to dimethylglycine methyl ester" (217). du Vigneaud et al. continue, "Because of the existence of this relatively stable N-methyl bond one is tempted to postulate the existence of some derivative of choline in which the methyl groups are similarly chemically labilized by a group more electronegative than the alcoholic hydroxyl." In an earlier communication (210) they had suggested that phosphorylation of choline might induce mobility of a methyl group. In this connection it may be mentioned that choline sulfate, $(CH_3)_3\overset{+}{N}CH_2CH_2OSO_2\overset{-}{O}$, which has a "betaine" structure, occurs in the mycelium of Aspergillus sydowi, and that fourteen strains of this organism were found to volatilize arsenic when cultivated on "Czapek's solution agar" containing arsenious oxide (202). The volatile arsenic compound was not identified, but from numerous analogies (see also 26) there is little doubt that it was trimethylarsine. It is at present, however, impossible to assess the significance of these interesting observations. Furthermore, the mobility of the methyl group of betaine observed by Willstätter (217) and recently studied by Challenger, Taylor, and Taylor (66) occurs at 200°C. or higher, and some preliminary work by Dr. C. Simons in the author's laboratory suggests that under similar conditions a methyl group of choline may also be mobile.

The work of the American authors, while establishing the occurrence of transmethylation in animals, does not at this stage exclude formaldehyde (of secondary origin) as an alternative route, nor enable us to decide between the two mechanisms in the case of mould methylations (see page 338). A possible bridge between the animal and the mycological problems might be furnished by a study of the elimination of selenium, doubtless as dimethyl selenide, in the breath

of animals which have received injections or oral doses of selenates or selenites. The production of an unpleasant odor in the breath of such animals has long been known (see 62). A garlic odor in the breath of workmen engaged in the extraction of selenium from electrolytic copper "slimes" has also been observed (76).

Schultz and Lewis (see 54) found after subcutaneous injection of sodium selenite into adult white rats that 17 to 52 per cent of the administered selenium was excreted by the lungs within 8 hr. The product was absorbed in sulfuric acid, but was not identified. The amount was not materially influenced by administration of either methionine or choline chloride. Absorption in a very small quantity of Biginelli's solution (mercuric chloride in dilute hydrochloric acid) as employed by Bird and Challenger (25, 25a) in mould experiments might have led to a rapid decision. Similarly Dudley (76) reported the elimination of selenium as a volatile compound in the urine after administration of sodium selenite to a horse. It was not identified. McConnell (54) found that after single subtoxic injections of selenate containing radioactive selenium into adult white rats, 3 to 10 per cent of the original dose was excreted by the lungs in 23 hr., and absorbed in a hydrobromic acid–bromine mixture. The excretion was chiefly by the kidney in a non-volatile, ether-insoluble form.

Once the volatile product—presumably dimethyl selenide—has been identified, it is to be hoped that the elimination of selenium in the breath after simultaneous administration of trideuteriocholine or trideuteriomethionine will be studied. Absorption in nitric acid and analysis of the resulting hydroxydimethylselenonium nitrate, $(CH_3)_2Se(OH)NO_3$ (62), might bring a decision regarding the mechanism of this process. Similar experiments could be carried out with sodium tellurite, but the identification of the dimethyl telluride which would presumably result might, owing to its ready oxidation, present difficulties (25).

An obvious extension of the work of du Vigneaud and his colleagues would be to add arsenite, selenite, or tellurite and a compound having one or more mobile deuteriomethyl groups to cultures of S. brevicaulis. It might then be possible to decide whether transmethylation, established for certain animal methylations, also holds for the mycological process. As already stated, it is at present impossible to decide upon this point, owing to insufficient evidence. In the author's opinion it will, probably, be very profitable to seek experimental confirmation of the transmethylation hypothesis. The mobile methyl group has undoubtedly acquired considerable biochemical significance in the last few years, whereas the formaldehyde theory has not received any further experimental support. As suggested on page 339, however, the possibility that the utilization of carbon dioxide produced by the moulds is concerned with the phenomenon should also be considered.

REFERENCES

(1) ABBOTT AND LEWIS: J. Biol. Chem. **131**, 479 (1939).

(2) ABBOTT AND LEWIS: J. Biol. Chem. **137**, 535 (1941).

(3) ABEL: Z. physiol. Chem. **20**, 253 (1894).

(4) ABEL AND BUTTENBERG: Z. Hyg. **32**, 499 (1899).

(5) ACKERMANN: Z. Biol. **59**, 17 (1912).

(6) ALDRICH: J. Exptl. Med. **1**, 323 (1897).

(7) Am. J. Physiol. **5**, 457 (1901).

(8) Analyst (The) **57**, 155, 163 (1932).

(9) ARMSTRONG AND ARMSTRONG: *The Glycosides*, p. 66. Longmans, Green and Company, London (1931).

(10) ASTWOOD: J. Pharmacol. **78**, 79 (1943).

(11) ASTWOOD: J. Am. Med. Assoc. **122**, 78 (1943).

(12) BAEYER: Ann. **107**, 285 (1858).

(13) BALFE, CHAPLIN, AND PHILLIPS: J. Chem. Soc. **1938**, 341.

(14) BALFE AND NANDI: J. Chem. Soc. **1941**, 70.

(14a) BARRENSCHEEN AND VALYI-NAGY: Z. physiol. Chem. **277**, 97 (1942).

(15) BASEDOW: Schmidt's Jahrbuch **52**, 89 (1846).

(16) BAUMANN: Biochem. Z. **54**, 30 (1913).

(17) BECKMANN: Pharm. Zentralhalle **37**, 557 (1896).

(18) BENNETT: Pharm. J. **129**, 387 (1932).

(19) BENNETT: Quart. J. Pharm. Pharmacol. **6**, 375 (1933).

(20) BERNHAUER AND SCHEUER: Biochem. Z. **253**, 11 (1932).

(21) VAN DEN BERGE: Thesis, "Beordeeling van de Waarde van Fungicide Stoffen voor Houtconserveering," p. 41, Delft, 1934.

(22) BERTRAM: Ber. **25**, 64 (1892).

(23) BIELSCHOWSKY: Proc. Biochem. Soc., xv (1943).

(24) BIGINELLI: Gazzetta **31** (1), 58 (1901).

(25) BIRD AND CHALLENGER: J. Chem. Soc. **1939**, 163.

(25a) BIRD AND CHALLENGER: J. Chem. Soc. **1942**, 574.

(26) BIRD AND CHALLENGER: J. Chem. Soc., forthcoming publication.

(27) BIRKINSHAW, FINDLAY, AND WEBB: Biochem. J. **36**, 526 (1942).

(28) BLACKBURN: Private communication.

(29) BLACKBURN: Thesis, "Studies on Methylation by *Penicillium brevicaule*, Leeds, 1938.

(30) BLOCH AND SCHOENHEIMER: J. Biol. Chem. **135**, 99 (1940).

(31) BLOEMENDAL: Arch. Pharm. **246**, 599 (1908).

(32) BLOUNT, OPENSHAW, AND TODD: J. Chem. Soc. **1940**, 286.

(33) BLYTH: *Poisons: Their Effects and Detection*, p. 588 (1884).

(34) Reference 33, pp. 544, 545.

(35) Brit. Chem. Abstracts **82**, 629 (1902).

(36) BROWNEN: Pharm. J. **6**, 561 (1876).

(37) BRUNEL: Thesis, "Le métabolisme de l'azote d'origine purique chez les champignons," Paris, 1936.

(38) BRUNEL: Compt. rend. **204**, 380 (1937).

(39) BRUNEL: Compt. rend. **206**, 858 (1936).

(40) BUNSEN: Pogg. Ann. **40**, 219 (1837).

(41) BUNSEN: Pogg. Ann. **42**, 145 (1837).

(42) BUNSEN: Ann. **24**, 271 (1837).

(43) BUNSEN: Ann. **31**, 175 (1839).

(44) BUNSEN: Ann. **37**, 1 (1841).

(45) BUNSEN: Ann. **42**, 14 (1842).

(46) BUNSEN: Ann. **46**, 1 (1843).

(47) BUTKEWITSCH AND FEDOROV: Biochem. Z. **207**, 302 (1929).

(48) CADET DE GASSICOURT: "Histoire d'une liqueur fumante tirée de l'arsenie," présenté à l'Academie Royale des Sciences . . . Jour. Troisième, 623 (1760).

(49) CARLSON: Z. physiol. Chem. **49**, 431 (1906).

(50) CARR AND PEARSON: J. Chem. Soc. **1938**, 282.

(51) CEVEY: Dissertation, p. 40, Lausanne, 1902.

(52) CHALLENGER: J. Soc. Chem. Ind. (Chemistry & Industry) **54**, 657 (1935).

(53) CHALLENGER: J. Soc. Chem. Ind. (Chemistry & Industry) **55**, 900 (1936).

(54) CHALLENGER: J. Soc. Chem. Ind. (Chemistry & Industry) **61**, 413, 456 (1942).

(55) CHALLENGER: J. Soc. Chem. Ind. (Chemistry & Industry) **61**, 399 (1942).

(56) CHALLENGER AND BLACKBURN: J. Chem. Soc. **1938**, 1872.

(57) CHALLENGER AND ELLIS: J. Chem. Soc. **1933**, 396.

(58) CHALLENGER AND ELLIS: J. Chem. Soc. **1935**, 396.

(59) CHALLENGER AND HIGGINBOTTOM: Biochem. J. **29**, 1757 (1935).

(60) CHALLENGER AND HIGGINBOTTOM: Biochem. J. **29**, 1763 (1935).

(61) CHALLENGER, HIGGINBOTTOM, AND ELLIS: J. Chem. Soc. **1933**, 95.

(62) CHALLENGER AND NORTH: J. Chem. Soc. **1934**, 68.

(63) CHALLENGER AND RAWLINGS: J. Chem. Soc. **1936**, 264.

(64) CHALLENGER AND RAWLINGS: J. Chem. Soc. **1937**, 868.

(65) CHALLENGER, SUBRAMANIAM, AND WALKER: J. Chem. Soc. **1927**, 200.

(66) CHALLENGER, TAYLOR, AND TAYLOR: J. Chem. Soc. **1942**, 48.

(67) CHANDLER AND DU VIGNEAUD: J. Biol. Chem. **135**, 223 (1940).

(68) CLARKE, GILLESPIE, AND WEISSHAUS: J. Am. Chem. Soc. **55**, 4571 (1933).

(69) COOK: *Chemistry and Cancer*, Royal Institute of Chemistry Lecture Monograph, London (1944).

(70) CZAPEK AND WEIL: Arch. exptl. Path. Pharmakol. **32**, 438 (1893).

(71) Daily Press: January 19–20, 1932.

(72) DAKIN: J. Biol. Chem. **1**, 271 (1905–6).

(73) DÉBUS: Ann. **72**, 18 (1849).

(74) DEHN: Am. Chem. J. **40**, 88 (1905).

(75) DREW: J. Chem. Soc. **1929**, 566.

(76) DUDLEY: Am. J. Hyg. **23**, 179, 183 (1936).

(77) DUFF: J. Brit. Wood Preserving Assoc. **5**, 69 (1935).

(78) DYER: Pharm. J. **129**, 559 (1932).

(79) DYER: J. Biol. Chem. **124**, 519 (1938).

(80) ELLIS: Private communication.

(81) EMDE: Naturwissenschaften **17**, 700 (1929).

(82) EMMERLING: Ber. **29**, 2729 (1896).

(83) EVANS, MANN, PEISER, AND PURDIE: J. Chem. Soc. **1940**, 1215.

(84) FALTIS AND HOLZINGER: Ber. **72**, 1443 (1939).

(85) FESTER AND BERTUZZI: Rev. facultad quím. ind. agr. (Univ. nacl. litoral, Santa Fé, Argentina) **5**, 85 (1936).

(86) FLECK: Z. Biol. **8**, 444 (1872).

(87) FOSSE: Compt. rend. **182**, 869 (1926).

(88) FOSSE: Compt. rend. **183**, 1114 (1926).

(89) FOSSE AND BOSSUYT: Compt. rend. **188**, 106 (1929).

(90) FOSSE AND BRUNEL: Compt. rend. **188**, 426 (1929).

(91) FOSSE, BRUNEL, AND DE GRAEVE: Compt. rend. **189**, 213 (1929).

(92) FOSSE, DE GRAEVE, AND THOMAS: Compt. rend. **195**, 1198 (1932).

(93) FOSSE AND HIEULLE: Compt. rend. **177**, 199 (1923).

(94) FOSSE, THOMAS, AND DE GRAEVE: Compt. rend. **198**, 1953, 2208 (1934).

(95) FRANKE: J. Nutrition **8**, 597 (1934).

(95a) FRIEDRICH AND MARVEL: J. Am. Chem. Soc. **52**, 376 (1930).

(95b) FRITZMANN: Z. anorg. Chem. **73**, 244 (1912).

(96) FUCHS: Z. Biol. **98**, 473 (1938).

(97) GLEAVE, HUGHES, AND INGOLD: J. Chem. Soc. **1935**, 236.

(98) GMELIN: Karlsruhen Zeitung, November, 1839.

(99) GMELIN: *Wirkungen . . . auf den tierischen Organismus*, p. 43. Tübingen (1824).
(100) GORDON AND JACKSON: J. Biol. Chem. **110**, 151 (1935).
(101) GOSIO: Arch. ital. biol. **18**, 253, 298 (1893).
(102) GOSIO: Arch. ital. biol. **35**, 201 (1901).
(103) GOSIO: Ber. **30**, 1024 (1897).
(104) GOSIO: Atti accad. Lincei **13**, I, 422 (1904).
(105) GOSIO: Atti accad. Lincei **13**, I, 642 (1904).
(106) GRIFFITH: Biol. Symposia **5**, 193 (1941).
(107) GRIFFITH AND MULFORD: J. Am. Chem. Soc. **63**, 929 (1941).
(108) GRIFFITH AND MULFORD: J. Nutrition **21**, 633 (1941).
(109) GRISCHKEWITSCH-TROCHIMOVSKI: Rozcniki Chem. **8**, 423 (1928).
(110) GUGGENHEIM: *Die biogenen Amine*, 3rd edition, pp. 31, 192. Basel (1940); Nordemann Publishing Company, New York (1940).
(111) Reference 110, pp. 106, 109.
(112) Reference 110, p. 177.
(113) Reference 110, pp. 79, 81.
(114) HAAS: Biochem. J. **29**, 1298 (1935).
(115) HAMPSHIRE: Pharm. J. **129**, 373 (1932).
(116) HANDLER, BERNHEIM, AND KLEIN: J. Biol. Chem. **138**, 211 (1941).
(117) HANSEN: Ann. **86**, 213 (1853).
(118) HEIGENER: Zentr. Bakt. Parasitenk. II, **93**, 81 (1935-6).
(119) HESS: Ber. **46**, 4104 (1913).
(120) HESS: Ber. **48**, 1886 (1915).
(121) HESS: Ber. **50**, 344, 385 (1917).
(122) HESS, EICHEL, AND VIBRIG: Ber. **50**, 351 (1917).
(123) HILDEBRANDT: Schriften Naturforsch. Ges. Danzig **12**, XXII (1907); abstracted in Zentr. Bakt. Parasitenk. II, **21**, 180 (1908).
(124) HILDEBRANDT: Beiträge Chem. Phys. Path. **7**, 433 (1906); **9**, 470 (1907).
(125) HIMSWORTH: Lancet **245**, 465 (1943); see also Editorial note, p. 483.
(126) HIS: Arch. exptl. Path. Pharmakol. **22**, 253 (1887).
(127) HOFMEISTER: Arch. exptl. Path. Pharmakol. **33**, 198 (1894).
(128) HORN: Z. physiol. Chem. **242**, 23 (1936).
(129) HORN: Z. physiol. Chem. **238**, 84 (1936).
(130) HUFF AND PERLZWEIG: J. Biol. Chem. **142**, 401 (1942).
(131) HUFF AND PERLZWEIG: J. Biol. Chem. **150**, 395 (1943).
(132) HUGHES: J. Chem. Soc. **1935**, 255.
(133) HUGHES AND INGOLD: J. Chem. Soc. **1933**, 1571.
(134) HUGHES AND INGOLD: J. Chem. Soc. **1935**, 251.
(135) HUGHES, INGOLD, AND PATEL: J. Chem. Soc. **1933**, 526.
(136) HUSS: Z. Hyg. **76**, 361 (1914).
(137) JAPHA: Dissertation, Halle, 1842.
(138) JOHNSON: J. Am. Chem. Soc. **59**, 1261 (1937).
(139) JONES: J. Chem. Soc. **1932**, 2284.
(140) KEESER: Heffter's *Handbuch der experimentellen Pharmakologie* (Ergänzungsband) **3-4**, 176 (1937).
(141) KEILIN AND HARTREE: Proc. Roy. Soc. (London) **B119**, 114 (1936).
(142) KINOSITA: Yale J. Biol. Med. **12**, 287 (1940).
(143) KLASON: Ber. **47**, 2634 (1914).
(144) KOFOID: *Termites and Termite Control*. University of California Press, Berkeley, California (1934).
(145) KOMORI *et al*: J. Biochem. (Japan) **6**, 21, 163 (1926).
(146) KREER: Am. Lumberman **1936**, 38 (January 4).
(146a) LAW: Can. J. Research **1**, 398 (1941).
(147) LETTS: Pharm. J. **9**, 405, 417 (1878).

(148) LEVI: Gazzetta **62,** 775 (1932).
(149) LEWIS AND TAGER: Yale J. Biol. Med. **13,** 111 (1940).
(150) LOEVENICH, FREMDLING, AND FÖHR: Ber. **62,** 2856 (1929).
(151) LOWRY AND GILBERT: J. Chem. Soc. **1928,** 3181.
(152) MAASSEN: Arb. kaiser Gesundh. **18,** 479 (1902).
(152a) MANN AND QUASTEL: Biochem. J. **31,** 869 (1937).
(153) MARTIN: Gazette medicale, p. 130 (February 13, 1847).
(154) McHENRY: Biol. Symposia **5,** 177 (1941).
(154a) McILWAIN: J. Chem. Soc. **1937,** 1705.
(155) MELLOR: *Comprehensive Treatise on Inorganic and Theoretical Chemistry,* Vol. XI,
      p. 30. Longmans, Green and Company, London (1931).
(156) MILNE AND RATTRAY: Pharm. J. **130,** 246 (1933).
(157) MILNE AND RATTRAY: J. Roy. Tech. Coll. (Glasgow) **3,** 332 (1934).
(158) MONTGOMERY: J. Am. Med. Assoc. **66,** 491 (1916).
(159) MOORE: Pharm. J. **129,** 451 (1932).
(160) MORIN: Pogg. Ann. **48,** 483 (1839).
(161) NAJJAR AND HOLT: Science **93,** 20 (1941).
(162) NAJJAR *et al.*: Proc. Soc. Exptl. Biol. Med. **48,** 413 (1941).
(163) NAJJAR AND WOOD: Proc. Soc. Exptl. Biol. Med. **44,** 386 (1940).
(164) NELSON, FITZHUGH, AND CALVERY: Can. J. Research **3,** 230 (1943).
(165) NEMEC: Biochem. Z. **112,** 286 (1920).
(166) NENCKI AND SIEBER: Monatsh. **10,** 526 (1889).
(167) NEUBERG AND GROSSER: Zentr. Physiol. **19,** 316 (1905–6).
(168) NEUBERG AND SCHWENK: Biochem. Z. **71,** 118 (1915).
(169) OTTO: Ber. **15,** 125 (1882).
(170) PECK AND HAUSER: J. Am. Chem. Soc. **60,** 2599 (1938).
(171) PERLZWEIG, BERNHEIM, AND BERNHEIM: J. Biol. Chem. **150,** 401 (1943).
(172) PLESCHTIZER AND PREOBRATENSKY: Arch. Gewerbepath. Gewerbehyg. **6,** 80 (1935).
(173) POHL: Arch. Exptl. Path. Pharmakol. **51,** 341 (1904).
(174) POLLER: Z. physiol. Chem. **217,** 79 (1933).
(175) POOL: Pharm. Weekblad **49,** 878 (1912).
(176) PUNTONI: Ann. igiene **27,** 293 (1917).
(177) RAISTRICK *et al.*: Trans. Roy. Soc. (London) **B220,** 78 (1931).
(178) RAISTRICK *et al.*: Trans. Roy. Soc. (London) **B220,** 61 (1931).
(178a) RAISTRICK *et al.*: Trans. Roy. Soc. (London) **B220,** 35 (1931).
(179) REISSERT: Am. J. Pharm. **56,** 177 (1884).
(180) RENALL: Biochem. Z. **55,** 296 (1913).
(181) RIESSER: Z. physiol. Chem. **86,** 440 (1913).
(182) ROBINSON: J. Chem. Soc. **111,** 877 (1917).
(183) ROSENHEIM: Proc. Chem. Soc., p. 138 (1902).
(184) SACCARDO: Sylloge fungorum omnium hucusque cognitorum **4,** 84 (1882–1889).
(185) SACHS: Ber. **54,** 1849 (1921).
(186) SANGER: Proc. Am. Acad. Arts Sci. **29,** 136 (1893).
(186a) SCHENK, SIMMONDS, COHN, STEVENS, AND DU VIGNEAUD: J. Biol. Chem. **149,**
      355 (1943).
(187) SCHERINGA: Pharm. Weekblad **65,** 677 (1928).
(188) SCHWEITZER: Biochem. Z. **78,** 37 (1916).
(189) SELMI: Ber. **7,** 1642 (1874).
(190) SHEARD AND TRIBLEY: Pharm. J. **129,** 367 (1932).
(191) SIMMONDS AND DU VIGNEAUD: J. Biol. Chem. **146,** 685 (1942).
(192) SIMONS: Private communication.
(193) SIMONS: Biochem. J. **35,** 749 (1941).
(194) SMITH AND CAMERON: Ind. Eng. Chem., Anal. Ed. **5,** 400 (1933).
(195) STETTEN: J. Biol. Chem. **140,** 143 (1941).

(196) STEVENSON, DOBRINER, AND RHOADS: Cancer Research **2**, 160 (1942).
(197) STRAW AND CRANFIELD: J. Soc. Chem. Ind. **55**, 40T (1936).
(198) STRECKER AND DANIELS: Ann. **462**, 186 (1928).
(199) SUMI: Biochem. Z. **195**, 161 (1928).
(200) TAMURA: Chem. Abstracts **19**, 2705 (1925).
(201) TAYLOR: Thesis, "Investigations on the Mechanism of Biological Methylation," p. 113, Leeds, 1937.
(202) THOM AND RAPER: Science **76**, 548 (1932).
(203) VALLANCE: *Text-book of Inorganic Chemistry*, Vol. 6, Part 4, p. 293. Newton Friend.
(204) VERNON: J. Chem. Soc. **117**, 86 (1920).
(205) VERNON: J. Chem. Soc. **117**, 894 (1920).
(206) VERONA: Boll. Fac. Agr. R. Univ. Pisa **13**, 62 (1937).
(207) VERVLOET: Pharm. Weekblad **1933**, 578.
(208) DU VIGNEAUD: Biol. Symposia **5**, 234 (1941).
(209) DU VIGNEAUD, CHANDLER, AND MOYER: J. Biol. Chem. **139**, 917 (1941).
(210) DU VIGNEAUD, CHANDLER, MOYER, AND KEPPEL: J. Biol. Chem. **131**, 57 (1939).
(211) DU VIGNEAUD, COHN, CHANDLER, SCHENCK, AND SIMMONDS: J. Biol. Chem. **140**, 625 (1941).
(212) DU VIGNEAUD *et al.*: J. Biol. Chem. **149**, 519 (1943).
(213) WAGNER: Biochem. Z. **64**, 72 (1914).
(214) WERNER: J. Chem. Soc. **111**, 844 (1917).
(215) WIECHOWSKI: Beiträge Chem. Physiol. **9**, 295 (1907).
(216) WIGREN: Ann. **437**, 285 (1924).
(217) WILLSTÄTTER: Ber. **35**, 584 (1902).
(218) WOOLEY AND PETERSON: J. Biol. Chem. **121**, 507 (1937).
(219) Zwolsche Courant (Holland), May 6, 1933.